DOCKET

SUPREME COURT
OF THE UNITED STATES

No. 09-1501
Title: Actavis, Inc., Petitioner
v.
Julie Demahy
Docketed: June 9, 2010
Linked with 09A919
Lower Ct: United States Court of Appeals for the Fifth Circuit
Case Nos.: (08-31234)
Decision Date: January 8, 2010
Questions Presented

---Date---	--------Proceedings and Orders----------
Mar 29 2010	Application (09A919) to extend the time to file a petition for a writ of certiorari from April 8, 2010 to June 7, 2010, submitted to Justice Scalia
Apr 6 2010	Application (09A919) granted by Justice Scalia extending the time to file until June 7, 2010
Jun 7 2010	Petition for a writ of certiorari filed. (Response due July 9, 2010)
Jun 7 2010	Appendix of Actavis, Inc. filed
Jun 11 2010	Waiver of right of respondent Julie Demahy to respond filed
Jun 23 2010	DISTRIBUTED for Conference of September 27, 2010
Jul 2 2010	Response Requested. (Due August 2, 2010)
Jul 30 2010	Brief of respondent Julie Demahy in opposition filed. (Distributed)
Aug 27 2010	Reply of petitioner Actavis, Inc. filed. (Distributed)
Nov 15 2010	DISTRIBUTED for Conference of December 3, 2010
Nov 15 2010	Supplemental brief of petitioner Actavis, Inc. filed. (Distributed)
Dec 6 2010	DISTRIBUTED for Conference of December 10, 2010
Dec 10 2010	Petition GRANTED. The petitions for writs of certiorari in No. 09-993 and No. 09-1039 are granted. The cases are consolidated and a total of one hour is allotted for oral argument.
Dec 23 2010	SET FOR ARGUMENT ON Wednesday, March 30, 2011
Dec 29 2010	Record received from U.S.C.A. for 5th Circuit. (1 box)
Jan 12 2011	Record received from U.S. D.C. for Eastern District of Louisiana. (1 Box)
Jan 20 2011	Consent to the filing of amicus curiae briefs, in support of either party or of neither party, received from counsel for the respondents. VIDEO
Jan 24 2011	Brief of petitioners PLIVA, Inc., et al. filed. VIDEO
Jan 24 2011	Consent to the filing of amicus curiae briefs, in support of either party or of neither party, received from counsel for petitioners PLIVA, Inc., Teva

Pharmaceuticals USA Inc., and UDL Labs. VIDED

Jan 24 2011 Consent to the filing of amicus curiae briefs in support of either party or of neither party received from counsel for petitioner Actavis Elizabeth LLC. VIDED

Jan 24 2011 Joint appendix filed. VIDED

Jan 24 2011 Brief of petitioners Actavis Inc. and Actavis Elizabeth LLC filed. VIDED

Jan 24 2011 Consent to the filing of amicus curiae briefs in support of either party or of neither party received from counsel for petitioner Actavis, Inc. VIDED

Jan 31 2011 Brief amicus curiae of Apotex Inc. filed. VIDED

Jan 31 2011 Brief amici curiae of Mylan Inc. Pharmaceuticals Inc., et al. filed. VIDED

Jan 31 2011 Brief amicus curiae of Generic Pharmaceutical Association filed. VIDED

Feb 4 2011 CIRCULATED. VIDED

Feb 23 2011 Brief of respondents Gladys Mensing and Julie Demaris filed. VIDED. (Distributed)

Mar 2 2011 Brief amici curiae of Public Citizen and AARP filed. VIDED. (Distributed)

Mar 2 2011 Brief amicus curiae of United States filed. VIDED. (Distributed)

Mar 2 2011 Motion of the Acting Solicitor General for leave to participate in oral argument as amicus curiae and for divided argument filed. VIDED

Mar 2 2011 Brief amicus curiae of Rep. Henry A. Waxman filed. VIDED. (Distributed)

Mar 2 2011 Brief amici curiae of Administrative Law and Civil Procedure Scholars filed. VIDED. (Distributed)

Mar 2 2011 Brief amici curiae of Marc T. Law, et al. filed. VIDED. (Distributed)

Mar 2 2011 Brief amici curiae of American Medical Association, et al. filed. VIDED. (Distributed)

Mar 2 2011 Brief amicus curiae of National Coalition Against Censorship filed. VIDED. (Distributed)

Mar 2 2011 Brief amicus curiae of Dr. Christy Graves filed. VIDED. (Distributed)

Mar 2 2011 Brief amici curiae of Torts Professors Mary J. Davis, et al. filed. VIDED. (Distributed)

Mar 2 2011 Brief amici curiae of National Conference of State Legislators filed. VIDED. (Distributed)

Mar 2 2011 Brief amici curiae of Minnesota, et al. filed. VIDED. (Distributed)

Mar 2 2011 Brief amicus curiae of American Association for Justice filed. VIDED. (Distributed)

Mar 2 2011 Brief amicus curiae of Constitutional Accountability Center filed. VIDED. (Distributed)

Mar 2 2011 Brief amici curiae of Jerome P. Kassirer, M.D., and Paul D. Stolley, M.D., M.P.H. filed. VIDED. (Distributed)

Mar 11 2011 Letter from counsel for PLIVA received. (Distributed). VIDED

Mar 18 2011 Motion of the Acting Solicitor General for leave to participate in oral argument as amicus curiae and for divided argument GRANTED.

Mar 23 2011 Reply of petitioners PLIVA, Inc., et al. filed. VIDED. (Distributed)

Mar 23 2011 Reply of petitioners Actavis Elizabeth LLC filed. VIDED. (Distributed)

Mar 30 2011 Argued. For petitioners: Jay P. Lefkowitz, New York, N.Y. For respondents: Louis M. Bograd, Washington, D.C., and Edwin S. Kneedler, Deputy Solicitor General, Department of Justice, Washington, D.C. (for United States, as amicus curiae.)

amicus curiae

PETITION FOR WRIT OF CERTIORARI

Supreme Court, U.S.
FILED

No. 09-_091501 JUN 7 - 2010

OFFICE OF THE CLERK

IN THE

Supreme Court of the United States

ACTAVIS, INC.,

Petitioner,

v.

JULIE DEMAHY,

Respondent.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Eleventh Circuit

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PETITION FOR WRIT OF CERTIORARI

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QUESTION PRESENTED

Are the states preempted under the Supremacy Clause of the Constitution from requiring additional safety information on a generic product label where the brand has not changed its label?

LIST OF PARTIES

The caption of the case contains the names of all parties to the appellate proceeding in the Fifth Circuit Court of Appeals.

CORPORATE DISCLOSURE STATEMENT

Actavis Group hf is a privately-held Icelandic company, and the parent corporation of Actavis Group PTC, ehf, which is the parent of petitioner Actavis Inc., a Delaware corporation. Actavis-Elizabeth, LLC, a subsidiary of Actavis Inc., is the successor to Purepac Pharmaceutical Co., Inc., which no longer exists. No publicly held corporation owns ten percent or more of Actavis Inc.'s stock.

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The decision of the Fifth Circuit Court of Appeals is reported at 593 F.3d 428 (5th Cir. 2010) and reprinted in the Appendix (App.___) at 1a-46a. The district court's decision is reported at 586 F. Supp. 2d 642 (E.D. La. 2008), and reprinted at App. 47a-91a.

JURISDICTION

The Fifth Circuit Court of Appeals rendered its decision on January 8, 2010. On April 5, 2010, Justice Scalia extended the time for petitioner to file a petition for a writ of certiorari to June 7, 2010. This Court has jurisdiction under 28 U.S.C. § 1254.

CONSTITUTIONAL, STATUTORY AND REGULATORY PROVISIONS INVOLVED

The pertinent provisions of U.S. Const., Art. VI, clause 2, 21 U.S.C. § 355 and 21 C.F.R. §§ 314.3, 314.70, 314.94, 314.97 and 314.150 are reproduced at App. 113a-131a.

INTRODUCTION

This petition, which arises from litigation seeking to hold a generic drug manufacturer liable under state products liability law for not adding safety information to the label of its product, is similar to the petitions in *Actavis Elizabeth, LLC v. Mensing*, No. 09-1039 (petition for cert. filed Feb. 25, 2010), and *Pliva, Inc. v. Mensing*, No. 09-993 (petition for cert. filed Feb. 19, 2010), on which this Court

recently requested the views of the Solicitor General. Review of these cases by this Court is appropriate because the lower courts have misinterpreted *Wyeth, Inc. v. Levine*, 129 S. Ct. 1187 (2009), disregarding crucial differences between the labeling responsibilities of generic drug manufacturers and those of manufacturers of branded drugs. *Wyeth* held that manufacturers of branded drugs can comply with a duty to warn imposed by state law by making a unilateral label change. 129 S. Ct. at 1196-99. Generic drug manufacturers cannot do the same because they must at all times adhere to the label of the branded drug.

The decision below squarely addressed generic drug manufacturers' ability to institute a label change, making this case an appropriate vehicle in which to resolve a question of urgent national importance. In *Mensing*, the Eighth Circuit declined to decide that issue, resolving the preemption issue on the alternative ground that a generic drug manufacturer may be able to harmonize its state and federal duties by merely proposing a label change to the Food and Drug Administration (FDA). *Mensing v. Wyeth, Inc.*, 588 F.3d 603 (8th Cir. 2009).

In addition to having been considered by the Fifth and Eighth Circuits, the issue of whether the Federal Food, Drug and Cosmetic Act (FFDCA) preempts state product liability claims against generic drug companies, based on an obligation to include safety information on their labels when the brand has not done so, is raised in cases currently pending in the Sixth and Ninth Circuits, and it has been decided by numerous district courts.

In general, the courts have read *Wyeth* too broadly, as if that decision swept away federal preemption for all drug product liability claims. The nearly uniform misapplication of *Wyeth* by the lower courts requires this Court's intervention now, before generic drug manufacturers are forced by the threat of liability to abandon their low-cost business model, which provides patients access to drugs at reduced prices as envisioned by Congress when it passed the Hatch-Waxman Amendments to the FFDCA (Hatch-Waxman).

STATEMENT

A. Regulatory Framework

1. New Drugs

The process of bringing a new drug to market is expensive and time consuming. Under the FFDCA, a new drug may not be marketed until FDA has approved a new drug application (NDA). 21 U.S.C. §§ 331(d), 355(a). Before an NDA is submitted, the manufacturer must conduct a range of preclinical investigations, obtain FDA authorization to conduct human clinical trials designed to establish safety and efficacy, and then conduct those clinical studies. 21 U.S.C. § 355(i); 21 C.F.R. § 312.20. Once all of these studies have been completed, the sponsor must submit an NDA, containing "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective." 21 U.S.C. § 355(b)(1)(A). According to a recent study, the research to obtain approval of a single new drug can cost close to $1

billion.[1] Because FDA will find a drug safe and effective only under labeled conditions of use, FDA must review the drug label as part of the NDA process. 21 U.S.C. § 355(a), (b)(1)(F), (c)(1)(A), (d).

After a drug is approved, the brand manufacturer's obligations continue. Manufacturers must maintain records, conduct additional testing as directed, and advise FDA of significant adverse health consequences that are reported following the drugs introduction to the market (adverse event reporting). 21 U.S.C. § 355(k)(1); 21 C.F.R. § 314.80.

Further, as this Court held in *Wyeth* (129 S. Ct. 1187), when new information about the safety of a drug becomes apparent to the brand manufacturer, the brand manufacturer has the ability and obligation to change its label. 21 C.F.R. § 201.80(e). Through the "Changes Being Effected" (CBE) process, the brand can make such a change as soon as FDA receives the brand's supplemental application; it need not await FDA approval. 21 C.F.R. § 314.70(c)(6)(iii)(A), (C).

2. Generic Drugs

In 1984, Congress enacted Hatch-Waxman to streamline the process by which companies obtain approval of generic versions of brand drugs once the brand patents have expired (as extended by Hatch-Waxman). H. R. Rep. No. 98-857, pt. 2 at 8-9 (1984), *as reprinted in* 1984 U.S.C.C.A.N. 2686, 2692-93. The principal goal of the Act was to make available

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[1] Christopher Paul Adams & Van Vu Brantner, *Spending on New Drug Development*, 19 Health Econ. 130 (2010).

low cost generic drugs. *Serono Labs., Inc. v. Shahala*, 158 F.3d 1313, 1316 (D.C. Cir. 1998). Unlike the brand sponsor, which must submit scientifically valid clinical trials demonstrating safety and efficacy in order to obtain approval, the generic applicant can "piggyback" on the safety and effectiveness information that the brand submitted and must show only that its product is the same as the brand. *Purepac Pharm. Co. v. FDA*, 354 F.3d 877, 879 (D.C. Cir. 2004).

Under the Act, FDA will approve a generic drug for marketing upon proof that the drug (1) has the same active ingredient(s) as; (2) has the same route of administration, dosage form and strength as; (3) *has the same labeling as*; and (4) is bioequivalent to, the brand drug. 21 U.S.C. § 355(j)(2)(A)(i-v) (emphasis supplied). In other words, the thrust of Hatch-Waxman is that the generic must demonstrate that its product is a copy of the brand in every significant respect, including its labeling, so that once approved the generic version can be substituted for the brand without a physician's intervention. *See* FDA, Approved Drug Products with Therapeutic Equivalence Evaluations, p. iv (30th ed. 2010). The generic manufacturer is neither required to conduct the clinical studies needed to obtain approval of the brand product nor expected to master the clinical data that supports the various claims made on the product's label. Instead, the obligation of the generic manufacturer is to make a product that is a true copy of the brand.

Although a generic manufacturer is required to submit any adverse event reports that it receives

after a generic drug is approved, the vast majority of such reports do not go to the generic manufacturer, but instead go directly to FDA or to the brand manufacturer. *See* FDA, Manual of Policies and Procedures, Center for Drug Evaluation and Research, Office of Generic Drugs, Handling of Adverse Experience Reports and Other Generic Drug Postmarketing Reports, MAPP 5240.8 (Nov. 1, 2005).

Generic drugs have the same labeling as their brand counterparts. 21 U.S.C. § 355(j)(2)(A)(v); 21 C.F.R. § 314.94(a)(8)(iii). This means that generic drugs must have the same warnings as the brand. If the brand does make a labeling change, it is the generic manufacturer's responsibility to mirror that change in its own label. *See* FDA, Guidance for Industry, Revising ANDA Labeling Following Revision of the RLD Labeling (May 2000) (ANDA Labeling Revision Guidance). If the brand does not make a labeling change, however, the generic manufacturer may not make a unilateral change to its own label. Making changes that render the generic label different from the label of its reference listed drug is prohibited by the statute and regulations that require the generic label to be the same as the brand label *at all times*. If a generic does not maintain the same label as the brand, FDA can remove the generic from the market. 21 C.F.R. § 314.150(b)(10).

Generic drugs are an important component of efforts to control healthcare costs. In the last decade (1999-2008), generic medicines saved the American

health care system more than $734 billion, with approximately $121 billion in savings in 2008 alone.[2]

B. Proceedings Below

Julie Demahy brought this action alleging that she suffered from tardive dyskinesia, a serious movement disorder, which she alleges was caused by the drug metoclopramide. At the time Demahy took metoclopramide, it was being sold under the brand name Reglan by Schwarz, which had purchased the NDA from Wyeth, Inc. in 2001, and under its generic name metoclopramide by Purepac Pharmaceutical Co., which was purchased by petitioner Actavis. Demahy alleges in her complaint that her physician prescribed metoclopramide to her for more than four years. App. 96a-97a.

Demahy also alleges that Wyeth, as a successor to A.H. Robbins, "expressly warranted to some physicians that Reglan and/or metoclopramide was safe in long-term use," App. 102a, even though such a claim by Wyeth would have been contrary to Reglan's explicit labeling, which limited use to 12 weeks duration.[3] Demahy claims that Actavis is

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[2] *See* IMS Health & Generic Pharm. Ass'n, *Economic Analysis, Generic Pharmaceuticals 1999-2008: $734 Billion in Health Care Savings* (May 2009), available at http://gphaonline.org/sites/default/files/$734%20Billion%20in%20Generic%20Savings%20(PhA.pdf.

[3] The Reglan label in effect during the relevant time can be found at www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory.

liable under Louisiana products liability law for failing to include warnings about the risk of tardive dyskinesia from prolonged use in addition to those on the Reglan label.

Actavis moved to dismiss all of Demahy's claims on federal preemption grounds. The district court held that Demahy's failure to warn claims were not preempted. Reviewing that decision as an interlocutory appeal under 28 U.S.C. § 1292, the United States Court of Appeals for the Fifth Circuit affirmed. While acknowledging that Hatch-Waxman required that Actavis' product have the same label as Reglan at the time it was approved, the Fifth Circuit held that, just like the brand manufacturer in *Wyeth*, Actavis could have changed its label after approval if there was new safety information and that therefore Demahy's claim was not preempted. App. 23a-33a.[4]

REASONS FOR GRANTING THE WRIT

I. THE FIFTH CIRCUIT INCORRECTLY DECIDED AN IMPORTANT QUESTION OF FEDERAL LAW THAT SHOULD BE SETTLED BY THIS COURT.

In *Wyeth*, this Court held that the manufacturer of a *branded* drug could comply with

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[4] The Court rejected Demahy's contention that Actavis could have communicated directly with physicians about the risks associated with prolonged use of metoclopramide without FDA approval. App. 34a-35a. The Court also held that Actavis could have proposed a labeling change to the FDA. *Id.* That issue is raised in the *Mensing* petitions, but Petitioner has limited this petition to the issue of preemption of a state requirement that the generic change its label where the brand has not.

both federal law governing labeling and a duty to warn imposed by state products liability law because the manufacturer could change the label unilaterally pending FDA approval under the CBE regulation, 21 C.F.R. § 314.70(c)(6)(iii)(A), (C). 129 S. Ct. at 1996-99. Contrary to the text of governing statutes and regulations, the Fifth Circuit held that manufacturers of generic drugs may also make unilateral label changes under the CBE regulation.

While the CBE regulation explicitly permits the brand manufacturers to add a warning to their labels without FDA approval, the FDA law and regulations explicitly *prohibit* a generic manufacturer from making any change, including the addition of a warning, to the label of its products, if that change causes its label to deviate from that of the brand. That prohibition makes it impossible for the manufacturer of a generic drug to satisfy a state jury's determination that it has a duty to add a warning not found on the label of the brand drug, preempting such state failure-to-warn claims.

The FFDCA and FDA's implementing regulations require a generic drug to have the same label as the brand. 21 U.S.C. § 355(j)(2)(A)(v); 21 C.F.R. § 314.94(a)(8)(iii).[5] One of the grounds for not approving a generic drug is that the labeling proposed for the drug is not the same. 21 U.S.C. § 355(j)(4)(G). Although the Fifth Circuit acknowledged that a generic drug label has to mirror the brand at the time of approval, it concluded that

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[5] The statute and regulations do permit certain differences in labeling that are not applicable here. *See* 21 U.S.C. § 355(j)(2)(A)(v); 21 C.F.R. § 314.94(a)(8)(iv).

the FDA's requirements for approving a generic drug cease to matter after approval. App. 16a-37a.

That conclusion is wrong: a generic drug is required to have labeling that is identical to the brand *at all times*. If the brand drug changes its labeling after a generic is on the market, the generic must revise its label. *See* ANDA Labeling Revision Guidance at 4. Likewise, even if FDA requires labeling changes for the brand, as it did when it revised the prescription drug label format, the generic must wait until the brand changes its label before making the changes. *See* Requirements on Content and Format of Labeling for Human Prescription Drugs and Biological Products, 71 Fed. Reg. 3922, 3928 (Jan. 24, 2006). If a generic does not maintain the same label as the brand, FDA can remove the generic from the market. 21 C.F.R. § 314.150(b)(10).

In concluding that the same labeling requirement applies only at the time of approval, the Fifth Circuit ignored a central FDA regulation that defines "abbreviated application". The term is defined as an "application described in 314.94 *including all amendments and supplements* to the application." 21 C.F.R. § 314.3 (emphasis added). Thus, the same labeling requirement set out in 21 C.F.R. § 314.94, which applies in the first instance to "[a]bbreviated applications", applies by reference to ANDA amendments and supplements. Any change made in a supplement, pursuant to the CBE regulation, is therefore subject to the same labeling requirement, *i.e.*, the labeling in the supplement must also mirror the brand label. Thus, a generic

drug manufacturer can invoke the CBE regulation, but only to conform the generic drug's label to a change already made by the brand.

The Fifth Circuit cites an FDA regulation, 21 C.F.R. § 314.97, which explicitly states that a generic drug applicant must comply with the CBE regulation, 21 C.F.R. § 314.70, to support its assertion that the generic manufacturer may unilaterally add warning information to its label. App. 26a-27a. While section 314.97 requires a generic drug manufacturer to use the CBE process to change its label to match a change in the brand label, the Fifth Circuit was wrong in finding that it provides any authority for the generic manufacturer to unilaterally change its label. As explained above, such unilateral changes are prohibited by sections 314.3 and 314.94(a)(8)(iii).

In *Wyeth*, this Court held that "it is not impossible for Wyeth to comply with its state and federal law obligations." 129 S. Ct. at 1204. According to this Court, "[t]he CBE regulation permitted Wyeth to unilaterally strengthen its warning." *Id.* at 1199. But generic manufacturers do *not* have the ability to unilaterally change their label in a manner that is different from the brand. It is legally impossible for them to satisfy a jury-imposed duty to add warnings that differ from the warnings on the brand label.

Nevertheless, even though prior to *Wyeth* the lower courts often held that the FFDCA preempted failure to warn claims against generic

manufacturers,[6] since the *Wyeth* decision, the lower courts have generally reached the opposite result. District courts have relied on the erroneous rationale adopted by the Fifth Circuit[7] or the incomplete rationale of the Eighth Circuit,[8] or they have left the reasoning unclear.[9]

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[6] *See, e.g., Gaeta v. Perrigo Pharms. Co.*, 672 F. Supp. 2d 1017, 1020-21 (N.D. Cal. 2009) (on motion for reconsideration); *Morris v. Wyeth, Inc.*, No. 1:07-CV-176-R, 2009 WL 736200 (W.D. Ky. Mar. 4, 2009), (denying reconsideration in light of *Wyeth* of 582 F. Supp. 2d 861, 868-69 (W.D. Ky. 2008)); *Bolin v. Smithkline Beecham Corp.*, No. 08-60523-CIV, 2008 WL 3286973, at *8 (S.D. Fla. Aug. 7, 2008); *Mensing v. Wyeth, Inc.*, 562 F. Supp. 2d 1056, 1063-64 (D. Minn. 2008), *rev'd*, 588 F.3d 603 (8th Cir. 2009).

[7] *Dorsett v. Sandoz, Inc.*, No. CV 06-7821 AHM (AJWAx), 2010 WL 1174204, at *17-18 (C.D. Cal. Mar. 26, 2010); *Vitatoe v. Mylan Pharms., Inc.*, Civil Action No. 1:08CV85, 2010 WL 1008788, at *15 (N.D.W. Va. Mar. 5, 2010); *Munroe v. Barr Labs., Inc.*, 670 F. Supp. 2d 1299, 1302-03 (N.D. Fla. 2009); *Stacel v. Teva Pharms. USA*, 620 F. Supp. 2d 899, 907 (N.D. Ill. 2009); *Bartlett v. Mut. Pharm. Co.*, 659 F. Supp. 2d 279, 296-305 (D.N.H. 2009).

[8] *Swicegood v. Pliva, Inc.*, No. 1:07-CV-1671-TWT, 2010 WL 1138455, at *6 (N.D. Ga. Mar. 22, 2010); *Weilbrenner v. Teva Pharms. USA, Inc.*, Civil Action No. 7.08-CV-23 (HL), 2010 WL 924915, at *7 (M.D. Ga. Mar. 10, 2010); *Fulgenzi v. Wyeth, Inc.*, 686 F. Supp. 2d 715, 722 (N.D. Ohio 2010); *Couick v. Wyeth, Inc.*, No. 3:09-cv-210-RJC-DSC, 2009 WL 4644394, at *3 (W.D.N.C. Dec. 7, 2009).

[9] It is unclear whether the district court considered any argument specific to generic manufacturers in *Schrock v. Wyeth, Inc.*, 601 F. Supp. 2d 1262 (W.D. Okla. 2009), which was decided a week after this Court's decision in *Wyeth v. Levine*. The decisions in *Pustejovsky v. Wyeth, Inc.*, No. 4:07-CV-103-Y, 2009 WL 3336032 (N.D. Tex. Sept. 4, 2009), and *Kellogg v. Wyeth*,

The lower courts' confusion about the proper scope of this Court's decision in *Wyeth* is itself a basis for granting certiorari.

II. PROMPT RESOLUTION OF THE QUESTION PRESENTED IS IMPORTANT TO PRESERVING THE ABILITY OF GENERIC DRUG COMPANIES TO CONTINUE TO PRODUCE LOW COST DRUGS.

This case is an appropriate vehicle to decide a question of national importance that should be settled by this Court, as the Court did with respect to branded drugs in *Wyeth*. Although a division among the Circuits would be an additional reason to grant review, this Court should not wait for the outcome of the appeals now pending before the Sixth and Ninth Circuits.[10]

Low-priced generic drugs now account for nearly 75% of prescription drugs sold in this country, and are an important component of efforts to control healthcare costs.[11] The Fifth Circuit decision,

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Inc., 612 F. Supp. 2d 437 (D. Vt. 2009), are unclear about the rationale for rejecting preemption.

[10] Argument in three pending appeals in the Sixth Circuit is scheduled on June 9, 2010. *Smith v. Wyeth, Inc.*, No. 09-5460 (6th Cir.); *Morris v. Wyeth, Inc.*, No. 09-5509 (6th Cir); *Wilson v. PLIVA, Inc.*, No. 09-5466 (6th Cir.). The Ninth Circuit has not yet scheduled argument in *Gaeta v. Perrigo Pharms. Co.*, No. 09-15001 (9th Cir. filed Jan. 6, 2009).

[11] IMS Health & Generic Pharm. Ass'n, *Economic Analysis, Generic Pharmaceuticals 1999-2008: $734 Billion in Health Care Savings* (May 2009), available at

however, threatens to undercut this success by imposing on the generic drug industry some of the burdensome and duplicative requirements that Hatch-Waxman sought to eliminate.

Congress designed a bifurcated regime for the manufacture of pharmaceuticals. As described above, companies that manufacture branded "pioneer" drugs must conduct extensive testing on the safety and effectiveness of their products prior to approval. Generic drug manufacturers are absolved from conducting such studies as long as they can demonstrate that their product is the same as the brand. Under the system designed by Congress, generic companies are not required to conduct, understand or interpret the clinical trials on safety and efficacy previously conducted by the brand manufacturer to obtain approval of the pioneer drug. Nor are they in possession of any post-marketing data generated in the years that the brand marketed its product without generic competition, which is often more than a decade.

Generic drug companies are required to report adverse events involving their products to the FDA, but they are not required to conduct any post-approval safety analyses. In fact, even after a generic drug is approved, the vast majority of adverse event reports go directly to FDA or the branded drug

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http://gphaonline.org/sites/default/files/$734%20Billion%20in%20Generic%20Savings%20GPhA.pdf (generic medicines saved the American health care system more than $734 billion between 1999 and 2008 with approximately $121 billion in savings in 2008 alone).

manufacturer.[12] The bottom line is that, under the statutory scheme, generic companies are not required to and do not monitor or analyze the information needed to determine if a labeling change is appropriate.

The parade of district courts that have already followed the Fifth and Eighth Circuits into error threatens to force a restructuring of the drug industry from one in which development and monitoring expenses are borne by pioneer drug manufacturers who receive an extended patent monopoly, to one in which generic drug manufacturers must develop their own analytical capabilities or must exit the business under threat of state tort liability. Generic drug manufacturers will be required to invest the substantial sums of money and time needed to analyze the underlying safety data and to collect and evaluate new data. Such an outcome could diminish the ability of generic drug companies to continue to sell their products at the substantially reduced prices currently charged, as Congress intended. *See* Brief of the Generic Pharm. Ass'n as Amicus Curiae, *Pliva, Inc. et al. v. Mensing*, *Actavis Elizabeth, LLC v. Mensing*, Nos. 09-993 & 09-1039, 16-20 (filed Apr. 21, 2010).

The facts of this case highlight the problem with holding the generic manufacturer liable. According to the Complaint, Wyeth as successor to A.H. Robbins, which manufacturered the brand,

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[12] *See* FDA, Manual of Policies and Procedures, Center for Drug Evaluation and Research, Office of Generic Drugs, Handling of Adverse Experience Reports and Other Generic Drug Postmarketing Reports, MAPP 5240.8 (Nov. 1, 2005).

"expressly warranted to some physicians that Reglan and/or metoclopramide was safe in long-term use, knowing that physicians would share the information with other physicians in their community . . . ." App. 102a. As explained above, metoclopramide was never approved for use of more than 12 weeks. *See* p. 7, *supra*. Since generic companies do not rely on traditional advertising to physicians,[13] there is no sound public policy reason to hold them liable for injuries allegedly resulting from unapproved uses that they did not promote.

The decisions of the lower courts create tremendous uncertainty that should be resolved by this Court so that the industry will know with clarity whether its companies are required to change their entire business model. The financial impact on this industry, which is so vital to patient care and efforts to control national health care costs, is by itself a sufficient reason to grant certiorari.

CONCLUSION

The petition for a writ of certiorari should be granted. If the Court does not grant certiorari in this case and grants certiorari in *Pliva, Inc. v. Mensing*, No. 09-993, and *Actavis Elizabeth, LLC v. Mensing*,

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[13] *See New Initiative to Improve Availability of Generics*, at www.fda.gov/ForConsumers/ConsumerUpdates/ucm151180.htm (last visited June 3, 2010); *Facts and Myths About Generic Drugs*, at www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/ucm167991.htm (last visited June 3, 2010).

No. 09-1039, it should hold this case until it issues its decision in the *Mensing* cases.

Respectfully submitted,

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APPENDIX

Supreme Court, U.S.
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IN THE OFFICE OF THE CLERK

Supreme Court of the United States

ACTAVIS, INC.,

Petitioner,

v.

JULIE DEMAHY,

Respondent.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Eleventh Circuit

APPENDIX TO PETITION FOR WRIT OF CERTIORARI

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APPENDIX A

IN THE UNITED STATES COURT OF APPEALS FOR THE FIFTH CIRCUIT

No. 08-31204

JULIE DEMAHY

Plaintiff-Appellee

v.

ACTAVIS, INC., Individually and as Successor in Interest of Purepac Pharmaceutical Company

Defendant-Appellant

Appeal from the United States District Court for the Eastern District of Louisiana

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Before KING, HIGGINBOTHAM, and CLEMENT, Circuit Judges.

PATRICK E. HIGGINBOTHAM, Circuit Judge:

This case presents one issue on appeal: whether the federal regulatory regime governing pharmaceuticals preempts state-law failure-to-warn claims against manufacturers of generic drugs. The

Supreme Court held, in *Wyeth v. Levine*, that such claims are not preempted against name brand drug manufacturers.[1] While not directing our result, it shadows our conclusion that the federal regulatory regime governing generics is also without preemptive effect.

I.

Julie Demahy's physician prescribed the drug Reglan to treat her gastroesophageal reflux. For the next four years, Demahy's pharmacy filled her prescription with the generic form of Reglan, metoclopramide, manufactured by Actavis.[2] Demahy alleges that its long-term ingestion caused her to develop tardive dyskinesia, a neurological movement disorder.

The Food and Drug Administration (FDA) approved Reglan in 1980, and Actavis began manufacturing generic metoclopramide thereafter. In 1985, the FDA required that Reglan's label be updated to include a warning regarding the risk of developing tardive dyskinesia. Actavis revised its labeling to comport with these changes to the Reglan label. There is no dispute that the generic drug's label was at all relevant times the same as Reglan's. In February 2009, the FDA issued a labeling revision for metoclopramide meant to warn of the risk of

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[1] 129 S. Ct. 1187 (2009).

[2] Formerly Purepac Pharmaceutical Company.

prolonged use, defined as use for more than 12 weeks.[3]

Demahy asserts claims of personal injury under the Louisiana Products Liability Act for, *inter alia*, failure to warn of the risks of neurological disorder after long-term use of metoclopramide.[4] Specifically, Demahy argues that Actavis ignored scientific and medical literature establishing a higher risk of developing tardive dyskinesia, failed to request a labeling revision from the FDA, failed to change the label itself even though no prior FDA approval was required, and failed to report safety information directly to the medical community.

Actavis moved to dismiss Demahy's claims, arguing that they rested on duties imposed by state law that could not be met under federal law—that they were conflict preempted. The district court denied the motion as to the failure-to-warn claims.[5]

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[3] Letter from Joyce Korvick, Deputy Dir. for Safety, Div. of Gastroenterology Products, Center for Drug Evaluation and Research, FDA, to NDA holders for Reglan, at 3 (Feb. 26,2009) ("Prolonged treatment (greater than 12 weeks) with metoclopramide should be avoided in all but rare cases where therapeutic benefit is thought to outweigh the risks to the patient of developing tardive dyskinesia.").

[4] LA. REV. STAT. 9:2800.51 *et seq.* The district court dismissed without prejudice Demahy's initial claims against defendants Wyeth, Inc., the manufacturer of brand-name metoclopramide, and Schwarz, Inc., another generic manufacturer, after Demahy's pharmacy records indicated she had taken only Actavis-manufactured metoclopramide.

[5] Actavis's 12(b)(6) motion also argued—successfully—that Demahy's fraud-on-the-FDA claims were conflict

Since then, one sister circuit—the Eighth[6]—has considered the issue, which has split a rapidly growing number of district courts;[7] it held that state

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preempted. The only claims at issue on appeal are those alleging a failure to warn.

[6] *Mensing v. Wyeth*, 588 F.3d 603 (8th Cir. 2009).

[7] District court cases finding state law preempted include *Gaeta v. Perrigo Pharm. Co.*, ___ F. Supp. 2d ____, 2009 WL 4250690 (N.D. Cal. Nov. 24, 2009) (order denying plaintiffs' motion for reconsideration); *Smith v. Wyeth*, 2009 WL 425032 (W.D. Ky. Feb. 20, 2009) (unpublished), *Morris v. Wyeth*, 642 F. Supp. 2d 677 (W.D. Ky. 2009), *Wilson v. Pliva*, 640 F. Supp. 2d 879 (W.D. Ky. 2009), *Masterson v. Apotex Corp.*, 2008 WL 3262690 (S.D. Fla. Aug. 7, 2008) (unpublished), and *Mensing v. Wyeth*, 562 F. Supp. 2d 1056 (D. Minn. 2008), preemption holding overruled by *Mensing v. Wyeth*, 588 F.3d 603 (8th Cir. 2009). Those finding no preemption include *Munroe v. Barr Labs., Inc.*, ___ F. Supp. ____, 2009 WL 4047949 (N.D. Fla. Oct. 15, 2009); *Bartlett v. Mutual Pharm. Co.*, ___ F. Supp. ____, 2009 WL 3126305 (D.N.H. September 30, 2009); *Stacel v. Teva Pharm.*, 620 F. Supp. 2d 899 (N.D. Ill. 2009), *Kellogg v. Wyeth*, 612 F. Supp. 2d 421 (D. Vt. 2008), *Tucker v. SmithKline Beecham Corp.*, 596 F. Supp. 2d 1225 (S.D. Ind. 2008) (reversing its earlier ruling dismissing the case on preemption grounds), *Barnhill v. Teva Pharm.*, 2007 U.S. Dist. LEXIS 44718 (S.D. Ala. 2007) (unpublished), and *Laisure-Radke v. Par Pharm., Inc.*, 2006 WL 901657 (W.D. Wash. March 29, 2006) (unpublished). *See also McKenney v. Purepac Pharm. Co.*, 167 Cal. App. 4th 72 (Cal. App. 2008) (finding no preemption) *Barhoum v. Barr Pharm., Inc.* (N.J. Super., L. Div., Aug. 1 2008) (unpublished) (same); *Kelly v. Wyeth, Inc.*, 22 Mass. L. Rep. 384 (Sup. Ct. 2007) (same).

Actavis also urges this court to consider *Colacicco v. Apotex, Inc.*, 521 F.3d 253 (3d Cir. 2008) as persuasive. *Colacicco*, a pre-*Levine* case, found FDA failure-to-warn preemption as to both generic and name brand manufacturers, relying entirely on the rationale rejected by *Levine*. The Supreme Court later vacated and remanded for further

tort law is not preempted.[8] Appeals involving materially identical preemption claims are now pending before the Sixth Circuit.[9] Our review here is de novo.[10]

II

All prescription drugs marketed in this country must first receive FDA approval. Manufacturers of new drugs must submit a new drug application (NDA) to the FDA that demonstrates the drug's effectiveness and safety for its intended use.[11] The 1962 Food, Drug and Cosmetics Act (FDCA) established this avenue for pioneer drugs, with the core objective of ensuring that drugs are both safe and effective;[12] the FDA has codified the NDA

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consideration in light of *Levine*. *Colacicco v. Apotex, Inc.*, 129 S. Ct. 1578 (2009). Unlike the instant case, the heightened labeling requirement allegedly required by state law in *Colacicco* had been *expressly considered and rejected* by the FDA. 521 F.3d at 269. Given the vacatur of the Third Circuit's opinion, as well as the case's factual dissimilarity, we find it neither applicable norpersuasive here.

[8] *Mensing*, 588 F.3d at 612.

[9] *Smith v. Wyeth*, No. 09-5460 (6th Cir.); *Wilson v. Pliva*, 09-5466 (6th Cir.); *Morris v. Wyeth*, 09-5509 (6th Cir.).

[10] *See Carden v. General Motors Corp.*, 509 F.3d 227, 230 (5th Cir. 2007) (citing *Frank v. Delta Airlines, Inc.*, 314 F.3d 195, 197 (5th Cir. 2002)).

[11] *See* Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17950 (1992) (outlining the NDA process).

[12] *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 142 (2000).

regulations at 21 C.F.R. Part 314. New drug approval requires, among other deliverables, the results of[13] successful clinical trials and labeling that accurately portrays the benefits and risks of the drug, as indicated by those trials and other data.[14] "Before approving an NDA . . . [the] FDA undertakes a detailed review of the proposed labeling, allowing only information for which there is a scientific basis to be included in the FDA-approved labeling."[15] The FDA will reject the proposed labeling if "based on a fair evaluation of all material facts, such labeling is false or misleading in any particular."[16]

Contrast this with the simpler, less demanding approval process required of generic drugs. In 1984, Congress passed the Hatch-Waxman Amendments to the FDCA, which altered the federal regulatory regime governing generics. Thanks to these Amendments, once a pioneer drug loses patent

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[13] 21 U.S.C. § 355(b)(1) (requiring certain specified data including "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use" and "a full list of the articles used as components of such drug"). Approval is assured absent specified grounds for denial, such as a failure to "include adequate tests . . . to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof" or "results of such tests [that] show [the] drug is unsafe for use under such conditions." 21 U.S.C. § 355(d).

[14] *See* 21 U.S.C. § 355; 21 C.F.R. § 314.105(b).

[15] 73 Fed. Reg. 49603, 49604 (2008).

[16] *See* 21 U.S.C. § 355; 21 C.F.R. § 314.105(b).

protection, a drug company may seek permission to market a generic version through a significantly simplified process, known as the abbreviated new drug application procedure, or ANDA.[17] ANDA drugs must be the "same as" a name brand drug that has already been approved by the FDA as to active ingredients, route of administration, dosage form, strength, and conditions of use recommended in the labeling.[18] Under Hatch-Waxman, generic drug manufacturers need not repeat the clinical work of their name brand counterparts, but instead must only establish the generic drug's bioequivalence with the name brand drug.[19] By avoiding "unnecessary," "wasteful," and "unethical" duplication of previously-performed human clinical trials,[20] Congress meant "to provide a careful balance between promoting competition among pioneer . . . and generic drugs, and encouraging research and innovation."[21] In turn, this increased competition, coupled with the elimination of "retesting" of a drug that has already been determined to be safe and effective,[22] would

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[17] *See* 57 Fed. Reg. 17950, 17951 (describing the Hatch-Waxman Amendments).

[18] 21 U.S.C. § 355(j)(2)(A)(iii).

[19] 21 U.S.C. § 355(j)(2)(A)(iv).

[20] H.R. Rep. No. 98-857, pt. 1, at 16, 1984 U.S.C.C.A.N. at 2649.

[21] Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28872, 28874 (proposed July 10, 1989). *See also Mead Johnson Pharm. Group v. Bowen*, 838 F.2d 1332, 1333 (D.C.Cir. 1988) (Hatch-Waxman's purpose "was to increase competition in the drug industry by facilitating the approval of generic copies of drugs.").

result in significant cost savings to the American public.[23] Indeed, the Congressional Budget Office estimated that generic drugs save American consumers between $8 billion and $10 billion each year.[24] Generic drugs now account for seven out of ten prescriptions filled in the United States.[25]

In their application, generic manufacturers must also show "that the labeling proposed for the new drug is the *same as* the labeling approved for the listed drug."[26] Applying to market a generic drug, then, requires "[a] statement that the applicant's proposed labeling is the same as the labeling of the reference listed drug except for" enumerated differences irrelevant here; without such a statement, the FDA will deny the application.[27]

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[23] H.R. Rep. No. 98-857, pt. 1, at 16, 17.

[25] *Mead Johnson*, 838 F.2d at 1333.

[24] *See* How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry, A Congressional Budget Office Study, July 1998.

[25] Susan Okie, Multinational Medicines—Ensuring Drug Quality in an Era of Global Manufacturing, 361 NEW ENG. J. MED. 737, 738 (2009).

[26] 21 U.S.C. § 355(j)(2)(A)(v) (emphasis added); 21 U.S.C. § 355(j)(4)(G).

[27] Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17950, 17985–86 (Apr. 28, 1992) (later codified at 21 C.F.R. §§ 314.94(a)(8)(iii)–(iv) (1993)).

III

The Supreme Court ruled in *Levine* that the federal regulatory regime governing pharmaceuticals does not preempt a state-law failure-to-warn claim against the manufacturer of a name brand drug. Actavis urges that generic drugs are different because the manufacturer of a name brand drug may change its label unilaterally—through the "changes being effected" (CBE) process—while seeking the FDA's approval of the change. According to Actavis, a generic manufacturer, in contrast, must produce the same drug and use the same label as the name brand drug manufacturer.

The *Levine* Court did rely in part on the availability of the CBE process to reject the claim—advanced by a name brand manufacturer—that it was "impossible . . . to comply with both the state-law duties underlying those claims and its federal labeling duties."[28] The Court explained that once the risk to consumers has become "apparent," triggering a state-law duty to warn of it, "the CBE regulation permit[s] [the manufacturer] to provide such a warning before receiving the FDA's approval."[29] Though "the FDA retains authority to reject labeling changes made pursuant to the CBE regulation," the Court declined to "conclude that it was impossible for [the manufacturer] to comply with both federal and state requirements" without "clear evidence that the

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[28] *Levine*, 129 S. Ct. at 1196.

[29] *Id.* at 1198.

FDA would not have approved a change" to implement the warning.[30]

Justice Breyer wrote separately "to emphasize the Court's statement that 'we have no occasion in this case to consider the pre-emptive effect of a specific agency regulation bearing the force of law'"[31] and to accent the FDA's ability to "determine whether and when state tort law acts as a help or a hindrance to achieving the safe drug-related medical care that Congress sought" through "lawful specific regulations describing, for example, when labeling requirements serve as a ceiling as well as a floor."[32] Because no such regulation was at issue in *Levine*, Breyer agreed with the majority that state law was not preempted.[33]

Actavis rightly points out that *Levine* is not the case before us. It does, however, carry important implications for Actavis's situation as well.

IV

Here, as in every preemption case, "[t]he purpose of Congress is the ultimate touchstone."[34] Congressional intent to preempt state law can either

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[30] *Id.*

[31] *Levine*, 129 S. Ct. at 1204 (Breyer, J., concurring) (quoting *id.* at 1203).

[32] *Id.*

[33] *Id.*

[34] *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996) (plurality) (internal quotation marks omitted).

be expressed in statutory language or implied in the aim and structure of federal law.[35] Implied preemption comes in two forms: field and conflict preemption. Field preemption is inferred where federal law is so pervasive that it leaves no room for state supplementation.[36] When Congress has not completely displaced the possibility of state regulation, preemption may nonetheless occur when state law "actually conflicts" with federal law.[37] This conflict might be with a federal statute or an "agency regulation with the force of law."[38] Actavis asserts that Demahy's claims are conflict preempted: that it is impossible to comply with both federal and state law,[39] or, alternatively that state law poses an unacceptable "obstacle to the accomplishment and execution of the full purposes and objectives of Congress."[40] More specifically, Actavis contends that

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[35] *Hillsborough County, Fla. v. Automated Med. Labs., Inc.*, 471 U.S. 707, 712–13 (1985).

[36] *Id.*

[37] *English v. Gen. Elec. Co.*, 496 U.S. 72, 79 (1990).

[38] *Levine*, 129 S. Ct. at 1200.

[39] *Crosby v. Nat'l Foreign Trade Council*, 530 U.S. 363, 372–73 (2000) (emphasis added). Instances where it is impossible to comply with both federal and state law are very rare. *Fla. Lime & Avocado Growers v. Paul*, 373 U.S. 132, 143 (1963).

[40] *Crosby*, 530 U.S. at 372–73; *see also Levine*, 129 S. Ct. at 1193–94. *But see id.* at 1204–06 (Thomas, J., concurring in the judgment) (questioning "far-reaching implied pre-emption doctrines" and explaining Thomas's increasing skepticism of the Court's "purposes and objectives pre-emption jurisprudence").

it is impossible to comply with both the federal regulatory regime governing generic drugs and the putative state-imposed duty to heighten warning labels, or that Louisiana law obstructs the goals of the FDCA, as amended by the Hatch-Waxman Amendments and implemented by FDA regulation.

Such a conclusion is not to be found lightly. As *Levine* reminded, "[i]n all pre-emption cases, and particularly in those in which Congress has legislated . . . in a field which the States have traditionally occupied," a court must begin this inquiry into congressional intent "with the assumption that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress."[41] "We rely on the presumption because respect for the States as 'independent sovereigns in our federal system' leads us to assume that 'Congress does not cavalierly pre-empt [state law].'"[42] Though there is ongoing disagreement among Supreme Court jurists as to if, when, and how this presumption applies—particularly in implied conflict preemption cases—five members of the *Levine* Court held that it applies to conflict preemption cases at least where, as here, the question is whether federal regulation of

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[41] *Levine*, 129 S. Ct. at 1194–95 (quoting Lohr, 518 U.S. at 485) (internal citations and quotation marks omitted); *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218, 230 (1947).

[42] *Levine*, 129 S. Ct. at 1195 n.3 (quoting *Lohr*, 518 U.S. at 485).

prescription drugs preempts state-law failure-to-warn claims.[43]

In this case, the bar to a finding of preemption is set even higher because federal law provides no remedy for an injured consumer. Preemption of state failure-to-warn claims would foreclose a remedy that was traditionally available and for which federal law provides no substitute. Courts have been particularly reluctant to find preemption in such cases without an unambiguous signal of congressional intent.[44] This is

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[43] *Levine*, 129 S. Ct. at 1195–96 & n.3 ("[T]he dissent argues that the presumption against pre-emption should not apply to claims of implied conflict pre-emption at all . . . but this Court has long held to the contrary."). *But see id.*, 129 S. Ct. at 1229 n.14 (Alito, J., dissenting) ("[I]t is not true that this Court has long applied a presumption against pre-emption in conflict pre-emption cases.") (internal quotation marks omitted), *see also Wells Fargo Bank of Texas, N.A. v. James*, 321 F.3d 488, 491 (5th Cir. 2003). Though Justice Thomas joined in the *Levine* majority's judgment, he declined to say whether a presumption against preemption should apply. *Levine*, 129 S. Ct. at 1208, n.2 (Thomas, J., concurring) ("Because it is evident from the text of the relevant federal statutes and regulations themselves that the state-law judgment below is not pre-empted, it is not necessary to decide whether, or to what extent, the presumption should apply in a case such as this one, where Congress has not enacted an express pre-emption clause."). In its initial brief (submitted prior to the Supreme Court's decision in *Levine*) Actavis argues that this "presumption against preemption" does not apply to conflict preemption cases. Similarly, it appears that each district court to have found failure-to-warn suits conflict-preempted has not applied the presumption against preemption. *See, e.g., Mensing*, 562 F. Supp. 2d at 1061.

[44] *Lohr*, 518 U.S. at 487 ("It is, to say the least, 'difficult to believe that Congress would, without comment, remove all means of judicial recourse for those injured by illegal conduct.'") (*quoting Silkwood v. Kerr-McGee Corp.*, 464 U.S. 238, 251

especially true in cases that involve health and safety concerns, because "[s]tates traditionally have had greater latitude under their police powers to legislate as to the protection of the lives, limbs, health, comfort, and quiet of all persons."[45] Moreover, Congress has already expressly preempted state failure-to-warn claims for some products governed by the FDCA—medical devices[46]—and its choice not do so for other FDA-regulated products militates further against a finding of preemption here.[47] In *Levine*, the Court found Congress's enactment of an express preemption for medical devices telling, particularly given the historic coexistence of state tort remedies and federal regulation of prescription drugs.[48] As the

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(1984)); *Bates v. Dow Agrosciences LLC*, 544 U.S. 431, 449 (2005) ("If Congress had intended to deprive injured parties of a long available form of compensation, it surely would have expressed that intent more clearly."). *See also Silkwood*, 464 U.S. at 263–64 ("Because the Federal Government does not regulate the compensation of victims, and because it is inconceivable that Congress intended to leave victims with no remedy at all, the pre-emption analysis . . . comfortably accommodates—indeed it compels—the conclusion that compensatory damages are not pre-empted . . .") (Blackmun, J., dissenting).

[45] *Lohr*, 518 U.S. at 485. *Cf. Altria Group, Inc. v. Good*, 555 U.S. ___, 129 S. Ct. 538, 543 (2008).

[46] *Riegel v. Medtronic, Inc.*, 128 S. Ct. 999, 1009 (2008). In 1997, Congress preempted certain state requirements concerning over-the-counter medications but expressly preserved product liability actions. *See* 21 U.S.C. §§ 379r(e), 379s(d).

[47] *Levine*, 129 S. Ct. at 1200.

[48] *Id.*

Supreme Court has repeatedly instructed, "[t]he case for federal pre-emption is particularly weak where Congress has indicated its awareness of the operation of state law in a field of federal interest, and has nonetheless decided to 'stand by both concepts and to tolerate whatever tension there [is] between them.'"[49]

V

Against this backdrop, Actavis first argues "that it would have been impossible for [it] to comply with the state-law duty to modify [its product's] labeling without violating federal law,"[50] i.e., that "'compliance with both federal and state [law] is a physical impossibility.'"[51] Requiring that the conflict be one of "physical impossibility" readily suggests that this is a "demanding defense."[52] Here, Actavis urges that federal law requires that it maintain at all times a label that is the "same as" the name brand's, thus preventing simultaneous compliance with a state law requiring additional warnings.

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[49] *Ronito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 166–67 (1989) (quoting *Silkwood*, 464 U.S. at 256 (1984)).

[50] *Levine*, 129 S.Ct. at 1199.

[51] *Fid. Fed. Sav. & Loan Ass'n v. de la Cuesta*, 458 U.S. 141, 153 (1982) (quoting *Fla. Lime & Avocado Growers, Inc. v. Paul*, 373 U.S. 132, 142–43 (1963)). *See also Barnett Bank of Marion County, N.A. v. Nelson*, 517 U.S. 25, 31 (1996) (explaining that impossibility conflict would exist "if the federal law said, 'you must sell insurance,' while the state law said, 'you may not'").

[52] *Levine*, 129 S. Ct. at 1193.

There is no dispute here that Hatch-Waxman proscribes the *approval of an application* to produce a generic drug with labeling that is not the "same as" that of the listed drug. Demahy acknowledges that a generic's label must initially conform to a listed drug's and she does not allege that Actavis is liable under state law for failure to warn adequately of the risks of tardive dyskinesia at the time of approval. Rather, she seeks to hold Actavis liable for failing to take steps to *change* the label *after approval* in order to provide adequate warning once additional risks emerged. And, while Congress plainly intended for a generic drug manufacturer to submit labeling identical to—or, the "same as"—the brand name drug when seeking ANDA approval, the statutory scheme "is silent as to the manufacturer's obligations after the ANDA is granted."[53]

Of course, this statutory silence does not end our preemption inquiry, because "state laws can be pre-empted by federal regulations as well as by federal statutes."[54] The regulations on which Actavis relies, however, do not purport to bar generic labeling modifications following initial approval. Instead, they require only that a generic's label initially conform to the listed drug's; if the label does not, these regulations provide that an ANDA application

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[53] *See Bartlett*, ___ F. Supp. 2d ___, 2009 WL 3126305, at *12 (quoting *Stacel*, 620 F. Supp. 2d at 907); *see also* 21 U.S.C. § 355(j)(2)(A)(v); 21 U.S.C. § 355(j)(4)(G).

[54] *Hillsborough County, Fla. v. Automated Med. Labs, Inc.*, 471 U.S. 707, 713 (1985).

will be denied. They do not address post-approval modifications at all.[55]

On the contrary, "through many amendments to the FDCA and to FDA regulations, it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. It is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market."[56] As for maintaining an adequate label, the regulatory framework makes plain that manufacturers—name brand and generic alike—must act to warn customers when they learn that they may be marketing an unsafe drug. For their part, generic manufacturers are subject to the

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[55] 21 C.F.R. § 314.94(a)(8)(i) (explaining that generic drug manufacturer must provide a copy of the currently-approved labeling for the listed name brand drug as part of its ANDA application); 21 C.F.R. § 314.94(a)(8)(iv) (requiring that, as part of its ANDA application, a generic manufacturer give a side-by-side comparison of its proposed labeling with the approved labeling for the listed drug, with all differences annotated and explained); 21 C.F.R. § 314.127(a)(7) (noting that the FDA will not approve an ANDA application if information submitted is "insufficient to show that the labeling proposed for the drug is the same as labeling approved for the listed drug"); 57 Fed. Reg. 17950, 17957 cmt. 20 ("An ANDA *applicant* who believes the labeling for a proposed drug product should differ from that approved for the reference listed drug should contact FDA to discuss whether labeling for both generic and listed drugs should be revised.") (emphasis added).

[56] *Levine*, 129 S. Ct. at 1197-98 (citing 21 C.F.R. § 201.80(e) and 21 C.F.R. § 314.80(b)). *See also* 21 C.F.R. § 314.80(b) (placing responsibility on the manufacturer for post-marketing surveillance).

requirement that their labeling "be revised . . . as soon as there is reasonable evidence of an association of a serious hazard with a drug."[57] Demahy claims

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[57] 21 C.F.R. § 201.80(e). This requirement applies to drugs, such as metoclopramide, that are not tethered to a new drug application or supplement submitted prior to July 2001. *See id.* § 201.56(b).

Congress once again revised the prescription drug regime in 2007, through the Food and Drug Administration Amendments Act. These amendments provide that, when a drug is no longer marketed by its pioneering manufacturer (the NDA holder), ANDA holders must submit a supplemental application proposing labeling changes to reflect new safety information identified by the agency, or to explain why no change is warranted. 21 U.S.C. §355(o)(4)(B). Congress was careful to remind, however, that this obligation does not "affect the responsibility" of a generic manufacturer holding an approved ANDA "to maintain its label in accordance with existing requirements, including subpart B of part 201" and the CBE provision. *Id.* at § 355(o)(4)(I). Here, also, the FDA intended—in apparent contradiction to the plain text of 21 C.F.R. § 201.80—to "affirm that a CBE supplement is appropriate to amend the labeling for an approved product only to reflect newly acquired information and to make it clear that a CBE supplement may be used to add or strengthen a contraindication, warning, precaution, or adverse reaction only if there is sufficient evidence of a causal association with the drug . . . ." 73 Fed. Reg. at 49604.

Though in this case the pioneering manufacturer (Wyeth) still markets the listed drug, this provision is instructive nevertheless. If, as Actavis contends, neither this provision nor the CBE process impose any "responsibility" on a generic manufacturer "to maintain its label," we are then left wondering why Congress would have deemed it necessary to clarify that the2007 Amendments did not alter that responsibility, when we assume, as we must, that "Congress is aware of existing law when it passes legislation." *South Dakota v. Yankton Sioux Tribe*, 522 U.S. 329, 351 (1998) (quoting *Miles v. Apex Marine Corp.*, 498 U.S. 19, 32 (1990) (internal quotation marks omitted)).

that Actavis failed to comply with this requirement despite reasonable evidence that long-term use of metoclopramide poses a serious hazard. Actavis responds that this requirement is on the name brand manufacturer alone, or that it is overridden as to generics, in light of the putative requirement that it conform to the name brand's label at all times.

FDA commentary supports the requirement—advanced by Demahy—that "at a minimum a generic manufacturer should alert the agency to any new safety hazard associated with its product."[58] First, in commentary accompanying the FDA's implementation of the Hatch-Waxman Amendments, the FDA stated: "After approval of an ANDA, if an ANDA holder [a generic manufacturer] believes that new safety information should be added, *it should provide adequate supporting information to FDA*, and FDA will determine whether the labeling for the generic and listed drugs should be revised."[59] Generic manufacturers must also follow the same record keeping and reporting of adverse drug experiences postmarketing as name brand manufacturers. As the FDA explained, "ANDA applicants [must] submit a periodic report of adverse drug experiences even if the ANDA applicant has not received any adverse drug experience reports *or initiated any labeling changes*."[60] At the very least,

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[58] *Mensing*, 588 F.3d at 609.

[59] 57 Fed. Reg. 17950, 17961 cmt. 40 (Apr. 28, 1992) (emphasis added).

[60] 57 Fed. Reg. 17950, 17965 cmt. 53 (Apr. 28, 1992) (emphasis added).

then, the FDA contemplates that generic manufacturers will initiate label changes in addition to echoing changes to the name brand label.

Nevertheless, Actavis points out that 21 U.S.C. § 355(e) "authorizes the withdrawal of approval of an application if 'there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof.' This provision applies to both [generic] and [listed] drug products."[61] Further, 21 C.F.R. § 314.150, explains that the FDA will initiate proceedings to withdraw approval for a generic drug if "the labeling for the drug . . . *is no longer consistent with* that for the listed drug . . . except for differences approved in the ANDA . . . ."[62] Actavis reads this language to prevent it from revising the label of its generic metoclopramide, because doing so would result in the FDA's withdrawal of approval.

The FDA promulgated § 314.150 in response to comments that it "should create a new provision authorizing the agency to withdraw an [ANDA] if the [ANDA] holder failed to modify its labeling to match labeling changes in the reference listed drug."[63] After being "revised . . . accordingly," the final version now "states that the ANDA applicant's failure to maintain drug labeling that is consistent with that of the listed

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[61] 57 Fed. Reg. at 17962 (quoting 21 U.S.C. § 355(e)).

[62] 21 C.F.R. § 314.150(b)(10) (emphasis added).

[63] 57 Fed. Reg. at 17970 cmt. 78.

drug may be grounds for withdrawing approval of the [ANDA]."[64]

Similarly, in response to a comment that the "FDA should create a mechanism to compel ANDA holders to revise their labeling to conform to the listed drug product once the ANDA is approved," the FDA observed that 21 U.S.C. § 355(e)(2) already "authorizes the withdrawal of approval of an application if 'there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in [its] labeling.'"[65] Because this provision applies to both listed and generic drug products and "an ANDA must have labeling that is the same as the . . . listed drug," the FDA explained that "a generic drug . . . whose labeling is inconsistent with the listed drug's labeling might not be considered safe and effective."[66] Given that, the FDA crafted § 314.150 "to permit the agency to withdraw approval of the ANDA if an applicant fails to maintain labeling in compliance with the requirements of the" Hatch-Waxman Amendments.[67]

The overarching import of these remarks suggests, as one district court put it, that "the purpose of [the] regulation was not to prevent a

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[64] *Id.*

[65] 57 Fed. Reg. 17950, 17961 (quoting 21 U.S.C. §355(e)(2)).

[66] *Id.*

[67] *Id.*

generic manufacturer from improving or strengthening its warnings. It was, instead, to ensure that the FDA could require a generic manufacturer to modify its labeling to match labeling changes in the reference listed drug."[68] In *Levine*, the Supreme Court found it "difficult to accept" that "the FDA would bring an enforcement action against a manufacturer for strengthening a warning."[69] Nor is "a drug . . . misbranded simply because the manufacturer has altered an FDA-approved label"; rather, the misbranding provisions concern the accuracy of the label's substance and the adequacy of its warnings and the FDA "contemplates that federal juries will resolve most misbranding claims."[70]

This is not to say that generic drug manufacturers—or any drug manufacturers, for that matter—are free to make whatever changes they see fit. Most labeling modifications must be pursued through a "major changes" procedure, which requires prior FDA approval before any modification takes place.[71] As the *Levine* Court observed, "[g]enerally speaking, a manufacturer may only change a drug label after the FDA approves a supplemental

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[68] *Bartlett*, ___ F. Supp. 2d. ____, 2009 WL 3126305, at *18 (quoting *Barnhill*, 2007 U.S. Dist. LEXIS 44718, at *13). *But see Mensing*, 562 F. Supp. 2d at 1062 (finding that this statement "underscore[s] the notion that the ANDA drug's label must remain the same as that of the listed drug").

[69] *Levine*, 129 S. Ct. at 1197.

[70] *Levine*, 129 S. Ct. at 1197; *see also* 21 U.S.C. § 355(e).

[71] 21 C.F.R. § 314.70(b)(2)(v); 21 U.S.C. § 356a(c)(1).

application."[72] A manufacturer may, however, "make certain changes to its label before receiving the agency's approval," through the so-called "changes being effected," or CBE, process delineated in 21 C.F.R. § 314.70(c)(iii).[73]

Accordingly, Demahy posits that Actavis could have complied with FDA regulations and state law by using either the CBE process, the "major changes" procedure (otherwise known as the prior approval process), or a third method—warnings sent directly to healthcare providers. A finding of preemption would require that all be foreclosed to generic manufacturers. We consider each in turn.

A. The "Changes Being Effected" Process

Where, as here, the requisite labeling change would "add or strengthen a contraindication, warning, precaution, or adverse reaction,"[74] to reflect "information not previously submitted to the [FDA]" and is based on "sufficient evidence of a causal association," it qualifies for the CBE process,[75]

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[72] 129 S. Ct. at 1196.

[73] *Id.*

[74] *Id.* (quoting 21 C.F.R. § 314.70(c)(6)(iii)(A)) (internal quotation marks omitted).

[75] 73 Fed. Reg. 49603, 49604 (2008) ("Expressly requiring that a CBE supplement reflect newly acquired information and be based on sufficient evidence of a causal association will help to ensure that scientifically accurate information appears in the approved labeling for such products."); 21 C.F.R. § 601.12(f)(2) (explaining that the CBE is

meaning the manufacturer "may make the labeling change upon filing its supplemental application with the FDA; it need not wait for FDA approval."[76] The district court focused much of its analysis on the availability of the CBE process to generic manufacturers.

"Just as nothing in the text of the Hatch-Waxman Amendments forbids a generic manufacturer from changing its drug's label from the listed version's post-approval,"[77] the CBE regulation also does not, on its face, distinguish between generic and name brand drug manufacturers; that is, it does not forbid a generic manufacturer from using the CBE process to unilaterally change a label. Located at 21 C.F.R. § 314.70, the regulation provides that "the holder of an approved application"—not just an approved new drug application—"may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change."[78]

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available only when the proposed change "reflect[s] newly acquired information"). 21 C.F.R. § 314.70(c)(6)(iii)(A)(requiring that a CBE be supported by "evidence of a causal association [that] satisfies the standard for inclusion in the labeling under 201.57"); 21 C.F.R. § 814.3(o) (defining "[n]ewly acquired information" as "data, analyses, or other information not previously submitted to the agency").

[76] *Levine*, 129 S. Ct. at 1196 (quoting 21 C.F.R. § 314.70(c)(6)(iii)(A)).

[77] *Bartlett*, 2009 WL 3126305 at *14.

[78] 21 C.F.R. § 314.70(c)(6).

Unsupported by the regulation's text, then, Actavis must seek support from FDA commentary for its argument that generic manufacturers cannot use the CBE process. Specifically, when the Agency revised the CBE regulation following the Hatch-Waxman Amendments, it reminded "ANDA applicants that, as noted in paragraph 4 above, the labeling for an ANDA product must, with few exceptions, correspond to that for the reference listed drug."[79]

At first glance, this provision seems to provide arguable support for Actavis's view: the comment, unlike others it cites, refers to "the labeling for an ANDA *product*," rather than "the labeling proposed for a product in an ANDA *application*" and thus could be read to mandate that a generic's labeling remain the "same as" the listed drug's after approval. A closer examination—one that accounts for the comment's reference to "paragraph 4"—indicates, however, that the FDA's explanation was still fixed on the pre-approval label.

"Paragraph 4" turns down a suggestion that the FDA "accept ANDA's with warnings or precautions in addition to those on the reference listed drug's label," by noting that "the applicant's *proposed labeling* [must] be the same as that of the listed reference drug" with exceptions not relevant here.[80] So, once again we encounter an admonition that the content of a generic drug's labeling during

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[79] 57 Fed. Reg. at 17955.

[80] Id. at 17953.

the ANDA approval process conform to that of the corresponding listed drug; there is no direction, however, as to what may happen *afterwards*. It would be a stretch then, in light of paragraph 4's cameo in the FDA's comment to the CBE regulation, to read it as Actavis would have us do, and expand the directive that "the labeling proposed for the drug [be] the same as the labeling approved for the listed drug," into the post-approval period, an undemanded play with displacement of traditional state regulation.[81]

In addition, these comments accompanied the only change that the FDA made to the CBE regulations when implementing the Hatch-Waxman Amendments: the addition of a paragraph requiring applicants to "comply with the patent information requirements under [21 U.S.C. §355(c)(2)]."[82] Actavis's preferred reading of these comments is not plausible unless we accept the proposition that the FDA would, in a minor and unrelated revision, express the novel view that generic manufacturers are altogether forbidden from using the CBE process.

On the other hand, what the FDA clearly did do to implement Hatch-Waxman cuts against Actavis's position, or at the very least muddies congressional and agency intent: it promulgated 21 C.F.R. § 314.97, entitled "Supplements and other

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[81] 21 U.S.C. § 355(j)(4)(G).

[82] 57 Fed. Reg. at 17983 (later codified at 21 C.F.R. § 314.70(e) (1993)).

changes to an approved abbreviated application."[83] This rule provides that ANDA applicants "shall comply with the requirements of §§ 314.70 and 314.71 regarding the submission of supplemental applications and other changes to an approved abbreviated application."[84] The requirements of § 314.70 include, of course, the CBE process. Had the FDA intended to deny generic manufacturers access to the CBE procedures, notwithstanding § 314.97's plain language, we might expect the FDA to say so, either in § 314.97 or in the CBE provision itself. If this was the FDA's intent—and the industry's understanding at the time—it passed over the opportunity to make that clear in these provisions promulgated in Hatch-Waxman's wake. As the regulations stand, however, we cannot tack the words "only when a listed drug manufacturer has first revised its label" onto the end of § 314.97—as Actavis's argument begs.

Nonetheless, Actavis insists that the CBE process is only available to generic manufacturers to implement changes already made to the name brand's label: in other words, that § 314.97 only requires that generics *follow* name brand labeling if and when a change is made by the name brand manufacturer. For that reason, Actavis says, the FDA

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[83] 57 Fed. Reg. at 17987. The FDA received no comments on this change.

[84] 21 C.F.R. § 314.97. We acknowledge that the CBE regulations appear at 21 C.F.R. § 314.70, which is located in Subpart B of Part 314. The FDA entitled Subpart B "Applications," while giving Subpart C the moniker "Abbreviated Applications."

rejected a comment suggesting that ANDA holders be required to submit drug labeling at periodic intervals to ensure that the generic label matched its listed counterpart. The FDA found such a procedure unnecessary because "existing reporting requirements at 21 C.F.R. § 314.70 [including the CBE provision] ensure that labeling changes are brought to FDA's attention in an appropriate and timely fashion."[85] The FDA will then "advise ANDA holders of changes to be made after approval, but postapproval changes resulting from the expiration of exclusivity or patent protection are the responsibility of the ANDA holder."[86] While this comment surely indicates that a generic drug manufacturer should use the CBE process to enact changes endorsed by the FDA, it does not say, however, that the process was not also intended to allow ANDA holders to act independently from the name brand manufacturers.

Actavis also directs us to the FDA's rejection of yet another comment as part of administrative implementation of Hatch-Waxman. This time, it is one that suggested empowering "ANDA applicants to deviate from the labeling for the reference listed drug to add contraindications, warnings, precautions, adverse reactions, and other safety-related information."[87] In response, the FDA reiterated that "the ANDA product's labeling must be the same as the listed drug's product labeling because the listed

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[85] 57 Fed. Reg. at 17961 cmt. 39.

[86] *Id.*

[87] 57 Fed. Reg. at 17961 cmt. 40.

drug product is the basis for ANDA approval."[88] Because "[c]onsistent labeling will assure physicians, health professionals, and consumers that a generic drug is as safe and effective as its brand-name counterpart," the FDA instructed "an ANDA applicant [who] believes new safety information should be added to a product's labeling . . . [to] contact FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised."[89]

Nothing in this response deviates from the now-familiar distinction between the near-unqualified ban on labeling differences pre-approval and their availability "after approval of an ANDA." During that latter period, "if an ANDA holder believes that new safety information should be added, it should provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised."[90]

Actavis maintains that this passage demonstrates that, for generic drugs, the FDA "decides whether a revision is necessary, not the drug manufacturer." We agree, but the FDA is the ultimate arbiter for *all* changes—whether prompted by a pioneer manufacturer or a generic one. *Every* submitted change requires FDA approval, even one that takes effect immediately through the CBE process. The FDA makes these approval decisions

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[88] *Id.*

[89] *Id.*

[90] *Id.*

"based on a comprehensive scientific evaluation of the product's risks and benefits under the conditions of use prescribed, recommended, or suggested in the labeling."[91] Through this review, the FDA is in effect and in fact "determin[ing] whether the labeling for the generic and listed drugs should be revised." This is no less true when the FDA reviews the change only after it has been made, as is the case with CBE changes. At best, then, this language is reason for pause, not for a conclusive reading, or a finding of impossibility preemption.

Lastly, Actavis emphasizes the FDA's recent statements suggesting that generics cannot use the CBE process and that federal law preempts state-law failure-to-warn claims brought against generics. Actavis first points to two amici briefs filed by the FDA in *Colacicco v. Apotex Corp.*, a case heard in the Eastern District of Pennsylvania[92] and then in the Third Circuit. [93] The briefs argued that Hatch-Waxman and implementing FDA regulations preempt state failure-to-warn claims as to both listed and generic drug manufacturers.[94] In so doing, the FDA took the position that generic manufacturers

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[91] 73 Fed. Reg. at 49604.

[92] *Colacicco v. Apotex, Inc.*, 432 F. Supp. 2d 514 (E.D. Pa. 2006).

[93] *Colacicco v. Apotex, Inc.*, 521 F.3d 253 (3d Cir. 2008).

[94] Brief of United States as *Amicus Curiae*, *Colacicco v. Apotex, Inc.*, C.A. No. 05-5500-MMB (E.D. Pa. filed May 10, 2006); Brief of United States as *Amicus Curiae*, *Colacicco v. Apotex, Inc.*, No. 06-3107 (3d Cir. filed Dec. 4, 2006).

could not utilize the CBE process at all.[95] The Third Circuit found the plaintiffs' failure-to-warn claims preempted.[96] The Supreme Court later decided *Levine*, and in light of that holding, granted certiorari in *Colacicco*, vacated the judgment of the Third Cicruit, and remanded for further consideration.[97] In response to *Levine*, the United States withdrew as amicus in *Colacicco* and notified the Third Circuit that the United States "does not take a position on whether [the state-law failure-to-warn claims] are preempted" and "has not yet conducted an examination of various preemption issues following the Supreme Court's decision in *Wyeth [Levine]* that would be necessary to inform a position of the United States in this case."[98] Now withdrawn, the FDA's amicus views are muted and we do not consider them.

Similarly, Actavis has recently lost another pillar of support. In its briefs, Actavis relies on a footnote in the FDA's proposed 2008 revision to the CBE regulations, which states that "CBE changes are not available for generic drugs approved under an ANDA under 21 U.S.C. 355(j). To the contrary, a generic drug manufacturer is required to conform to

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[95] *Id.* at 7–8, 18.

[96] *Colacicco*, 521 F.3d at 276.

[97] *Colacicco v. Apotex*, No. 08-437 (Mar. 9, 2009).

[98] Letter from Sharon Swingle, U.S. Department of Justice - Civil Division, Appellate, to Marcia M. Waldron, Clerk, United States Court of Appeals for the Third Circuit (Apr. 28, 2009).

the approved labeling for the listed drug."[99] But the final version of the rule omits this footnote's language. In fact, the final rule—which seeks to "affirm that a CBE supplement is appropriate . . . only to reflect newly acquired information . . . and [when] there is sufficient evidence of a causal association with the drug"—is virtually silent as to generics altogether.

The final rule does, however, specifically note that the FDA is "amending its regulations regarding[100] changes to an approved [name brand] application." Noting this statement, Actavis points out that the rule does not mention that the changes affect generic applications as well. It then posits that this omission is a sign that the CBE process simply does not apply to generics.

We might agree absent three salient insights. First, in its commentary to the final version of the regulation, the FDA removed the footnote that explicitly stated what Actavis asks this court to now hold: that the CBE process does not apply to generics. Second, these regulations were promulgated prior to the Supreme Court's decision in *Levine* and since that time, the FDA has withdrawn its amicus in *Colacicco*, as part of an apparent reconsideration of its preemption position. Lastly, the 2008 final rule mentions generics only once—in a citation after a sentence that reads: "The agency has clarified by regulation and guidance the types of supplements

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[99] 73 Fed. Reg. at 2849 n.1.

[100] 73 Fed. Reg. at 49604.

that should be filed to satisfy a sponsor's obligations to change a drug's labeling . . . ." In support of this statement, the FDA cites 21 C.F.R. § 314.70 (which contains the CBE regulation) and a document entitled "Guidance for Industry: Changes to an Approved NDA or ANDA," produced in November 1999. The guidance document notes that "[a]ll labeling changes for ANDA products must be consistent with [21 U.S.C. § 355(j)]," but otherwise does not distinguish between label changes made by pioneer manufacturers and their generic counterparts.[101]

Without explicit reference to the use of the CBE process by generic manufacturers, we decline to read in a bar to its use. The FDA's "earlier position," either as amicus or commentator, is instead "deprived of all claim to deference, by the fact that it is no longer the agency's position."[102]

B. *Prior Approval Process*

Nor does anything in the FDCA or Hatch-Waxman Amendments explicitly forbid generic manufacturers from proposing a label change through the so-called prior approval process.[103] While FDA regulations provide for permissive use of

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[101] Guidance for Industry: Changes to an Approved NDA or ANDA, at *24 (November 1999). The guidance document refers to section 505(j) of the FDCA, which is codified at 21U.S.C.§ 355(j).

[102] *Riegel v. Medtronic, Inc.*, 128 S. Ct. 999, 1009 (2008).

[103] 21 C.F.R. § 314.70(b)(2)(v)(A).

the CBE process for warning enhancements, and the prior approval process is required for "major changes," there is no indication of an agency policy, let alone congressional intent, to prevent generic manufacturers from proposing any and all labeling changes—no matter the significance of the change—through the prior approval process. Rather, the regulations governing labeling changes repeatedly use the nonrestrictive phrase "[t]hese changes include, but are not limited to" in describing the changes manufacturers may propose through each type of supplement.[104] Indeed, manufacturers are *required* to use the prior approval process for most "labeling changes." [105]

C. *"Dear Doctor" Letters*

In addition to the CBE and prior approval processes, Demahy posits that Actavis could have satisfied its state-law duty to warn by communicating directly with doctors, through a "Dear Doctor" letter. These letters—addressed to medical professionals and intended to explain the risks associated with prolonged use of metoclopramide—would also be subject to FDA regulation because they fall within the agency's broad definition of "labeling." [106] But, when promulgating its labeling regulations well before the Hatch-Waxman Amendments, the FDA

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[104] *Id.* at §§ 314.70(b)(2), (c)(2), (d)(2).

[105] *Id.* at § 314.70(b)(2)(v)(A).

[106] 21 C.F.R. §§ 202.1(1), (2); *see also* 21 C.F.R. § 200.4 (regulating content and appearance of mailings about drugs to physicians).

made clear that the requirements "do not prohibit a manufacturer . . . from warning health care professionals whenever possibly harmful adverse effects associated with the use of the drug are discovered."[107]

Thus, though generic manufacturers cannot send "Dear Doctor" letters without prior FDA approval, they can suggest that the FDA send such letters on their behalf;[108] the FDA will then send letters out if it determines that they are a necessary part of a risk evaluation and mitigation strategy.[109] Under Louisiana law, a drug manufacturer may discharge its duty to warn through notice to the prescribing physician.[110]

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[107] 44 Fed. Reg. 37434, 37447 (June 26, 1979).

[108] 21 U.S.C. § 355-1(i)(2) (establishing this process as part of the 2007 amendments to the FDCA). Although this process was not in effect when Demahy took metoclopramide, the FDA's later endorsement of it provides support for Actavis's contention that Congress did not intend that generic manufacturers send out "Dear Doctor" letters independently. Although "[o]ccasionally, drug manufacturers and distributors mail important information about their drugs to health care professionals" with or without FDA involvement, longstanding FDA instructions for these mailings are directed at pioneer drug companies. NDAs: "Dear Healthcare Professional" Letters (July 2, 2003), *available* at http://www.fda.gov/cder/mapp/6020.10.pdf.

[109] *Id.*

[110] *See Stahl v. Novartis Pharm. Corp.*, 283 F.3d 254, 266 (5th Cir. 2002) (applying Louisiana law); *see also Marks v. OHMEDA, Inc.*, 2003-1446, p. 11 (La. App. 3 Cir. 3/31/04); 871 So. 2d 1148, 1157; *Mikell v. Hoffman-LaRoche, Inc.*, 94-0242, pp. 7–8 (La. App. 1 Cir. 12/22/94); 649 So. 2d 75, 79–80.

Of the three avenues for complying with both state and federal law that Demahy identifies—the CBE process, the prior approval process, and letters sent directly to healthcare providers—each shares the same fundamental attributes: the manufacturer bears primary responsibility for maintaining its label consistent with safe and effective use of its product; when reports indicate that a label requires revision, the manufacturer must alert the FDA and provide supporting scientific data; and the FDA then makes the decision whether such a labeling change is supported by science. Even though with the CBE process, the decision is made after the label has been changed, the key feature remains: the FDA is still the final arbiter of labeling changes, while the manufacturer retains primary responsibility for the content of its label. The federal interest is in maintaining safe and effective labeling that is consistent across name brand and generic bioequivalent versions of the same drug. *Who* prompts the FDA to consider necessary changes to that shared label is immaterial.

At best, Actavis has demonstrated that even an interpretation of the CBE process most favorable to Actavis (and one that fails to persuade this court) is decidedly equivocal. Yet, equivocation falls short of the "clear and manifest purpose of Congress" required for a finding of preemption.[11] Even assuming that the CBE regulation cannot be used by

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[11] *Levine*, 129 S. Ct. at 1195 (quoting *Lohr*, 518 U.S. at 485).

an ANDA holder to amend its label without FDA pre-approval, *Levine*'s principles still apply with full force, and we agree with Demahy that generic drug manufacturers may use two other means of complying with both federal and state law—the prior approval process and correspondence sent directly to healthcare providers.

Though most courts to have considered the question—including the one below—focus on the CBE process, the CBE regulation was not the exclusive, or even the primary, basis for rejecting preemption in *Levine*. Rather, the Court explained that the brand name drug manufacturer's quest for preemption was grounded in a "more fundamental misunderstanding" of the regulatory regime: that the "FDA, rather than the manufacturer, bears primary responsibility for drug labeling."[112] As we have seen, the opposite is true: "a central premise of federal drug regulation [is] that the manufacturer bears responsibility for the content of its label at all times."[113]

Actavis urges that Congress intended to preempt state law because FDA regulations do not impose a duty on generic manufacturers to change their drug labels. This argument does not address the question we must answer. Preemption is not found because state law imposes duties and federal law does not. We look instead to the state-law imposition of duties, and to whether those duties make simultaneous compliance with federal law

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[112] *Id.* at 1197.

[113] *Id.* at 1197–98.

impossible. What the FDA might have done once Actavis suggested these changes is immaterial to the imposition of liability; *Levine* makes plain that uncertainty about the FDA's response makes federal preemption less likely: "absent clear evidence that the FDA would not have approved a change to [the drug's] label, we will not conclude that it was impossible for the [the manufacturer] to comply with both federal and state requirements."[114] The record here contains nothing, let alone "clear evidence," that suggests the FDA would have rejected a labeling proposal from Actavis. In fact, as discussed, the FDA mandated earlier this year that manufacturers of metoclopramide revise their labels to disclose further risks of tardive dyskinesia associated with long-term use.[115]

Finally, Actavis's use of Justice Breyer's concurrence in *Levine* is here unavailing: he said *if* an agency sets a floor and a ceiling, its actions may very well enjoy preemptive effect. No such regulation bearing the force of law is before us, while the FDA's retreat from its earlier position on preemption and the use of the CBE provision casts further doubt on Actavis's argument. That being said, had the FDA gone further than Justice Breyer would require and specifically examined the risk of long-term use of metoclopramide at the time that Demahy's cause of

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[114] *Id.* at 1198.

[115] Letter from Joyce Korvick, Deputy Dir. for Safety, Div. of Gastroenterology Products, Center for Drug Evaluation and Research, FDA, to NDA holders for Reglan, at 3 (Feb. 26, 2009)

action arose, the argument for preemption would be on surer footing.[116]

VI

Even if compliance with state and federal law is not "impossible," state law is nonetheless preempted if it stands as an "obstacle to the accomplishment and execution of the full purposes and objectives of Congress" as embodied in the Hatch-Waxman Amendments and the FDCA.[117] Here, if preemption is to be found, two additional conclusions necessarily follow: first, that Congress intended the name brand drug manufacturer to bear the sole

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[116] *See Dusek v. Pfizer, Inc.*, No. Civ. A. H-02-3559, 2004 WL 2191804, at *10 (S.D. Tex. Feb. 20, 2004) (unpublished) ("The Court does not hold that FDA drug approvals in general preempt failure to warn claims. The Court merely rules that permitting Plaintiffs' claim would be authorizing judicially what the FDA already has expressly disallowed. . . . In the face of numerous contentions from several different sources that [the drug] should contain a warning that [it] can cause suicide, the FDA has consistently determined no such explicit causation admonition is justified scientifically. . . . Therefore, on the specific facts of this case. . ., Plaintiffs' failure to warn claim is preempted because it is in direct, actual conflict with federal law."). *Cf. Perry v. Novartis Pharm. Corp.*, 456 F. Supp. 2d 678, 686–87 (E.D. Pa. 2006)(relying on the fact that the FDA had made no conclusive determination on the specific risk and label at issue, prior to the time the cause of action arose, in holding that the plaintiff's failure-to-warn claim was not preempted). *See generally* Catherine M. Sharkey, *Products Liability Preemption: An Institutional Approach*, 76 GEO. WASH. L. REV. 449, 513–20 (2008) (advocating for the approaches taken in *Dusek* and *Perry*).

[117] *Crosby*, 530 U.S. at 372–73.

burden of coping with incipient risks, even when it has ceased manufacturing the drug and left the market to generics; and two, that Congress intended either that the name brand manufacturer be liable for *all* failure-to-warn claims—even those arising out of the use of generic substitutes—or, that the injured plaintiff be left with no remedy. In assessing congressional objectives, these corollaries cannot be put aside.

Compliance with Louisiana's failure-to-warn law, so says Actavis, will necessarily burden generic manufacturers with duplicative studies, trials, and other data-gathering exercises, all putative prerequisites to placing generic companies on notice that label changes are warranted. These burdens, if imposed, would no doubt drive up the development costs, and thus, the market price, of generic drugs—thwarting a key tenet of Hatch-Waxman "to make available more low cost generic drugs by establishing a generic drug approval procedure."[118]

But what Louisiana law would require of generic drug companies does not inevitably impose significant investment of time and money. For one, Actavis fails to identify any statutory or regulatory provision that obligates manufacturers to justify labeling changes through their own clinical trials or other similarly onerous efforts.[119] Yes, requests to

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[118] H.R. Rep. No. 98-857, pt. 1, at 14, 1984 U.S.S.C.A.N. at 2647.

[119] *See* 21 U.S.C. § 356a (containing no such requirement); 21 C.F.R. § 314.70 (same); *see also Bartlett*, 2009

the FDA for label changes must be buttressed with scientific evidence, but nothing indicates that the evidence must be—as a matter of regulatory prescription or scientific reliability—acquired through the manufacturer's own clinical tests. As FDA regulations make plain, the regulatory regime contemplates that drug companies will effect labeling changes without conducting new clinical trials: "labeling shall be revised to include a warning as soon as there is reasonable evidence of a serious hazard with a drug; *a causal relationship need not have been proved.*"[120] The FDA expects that such "reasonable evidence" might be derived from, among other sources, "new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses)."[121] While clinical studies, then, *may* be used to support labeling changes, they are in no way prerequisites to those changes. When the FDA itself mandated an enhanced warning for metoclopramide in early 2009,

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WL 3126305, at *24 (noting the absence of any such requirement).

[120] 21 C.F.R. § 201.80(e); *see also* 21 C.F.R. § 314.70(c)(6)(iii) (a CBE may be used "[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling under [21 C.F.R.] § 201.57(c)"); *Id.* at § 201.57(c)(6) (explaining that evidence must be "reasonable" in order to change a label's warnings and precautions); *Id.* at § 201.57(c)(7) (explaining that there must be "some basis to believe" in order to change a label's discussion of adverse reactions).

[121] 73 Fed. Reg. at 49604.

it did not conduct its own studies, but referenced studies published elsewhere.

Actavis concedes that generic manufacturers already must report "each adverse drug experience that is both serious and unexpected . . . as soon as possible but in no case later than 15 calendar days of initial receipt of the information by the applicant,"[122] and every other "adverse drug experience . . . at quarterly intervals, for 3 years from the date of approval . . . and then at annual intervals."[123] The FDA also requires that generics "develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA."[124] In *Levine*, the Supreme Court found that multiple reports of adverse drug experiences provided the substantiation necessary to justify a request for a heightened warning.[125]

At least in the case of metoclopramide, it seems, the allegedly higher risk of long-term use was noted in medical literature beginning in the 1980s and 1990s.[126] Even if state law prompts Actavis to alert the FDA to this information, Actavis has

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[122] 21 C.F.R. § 314.98 (referencing § 314.80); *Id.* at § 314.80(c)(1)(i).

[123] 21 C.F.R. § 314.80(c)(2)(i).

[124] 21 C.F.R. § 314.80(b).

[125] *Levine*, 129 S. Ct. at 1197.

[126] *See, e.g., Kelly v. Wyeth*, 2007 WL 1302589, at *2 n.7 (Mass. Super. 2007).

provided no evidence that such collection and analysis of existing data and conclusions would result in significant additional expenditures.

Stepping back, the duty to warn is, in general terms, predicated on the superior knowledge of the manufacturer.[127] In the world of prescription drugs, a pharmaceutical company manufactures, and the FDA approves, a branded drug only after extensive research and testing. Pioneer drug manufacturers thus develop superior knowledge of their product, and the duty to warn is more fairly imposed, as it was in *Levine*. Conversely, generic manufacturers undertake limited research efforts thanks to Hatch-Waxman. They can obtain approval for their copycat drug and label with the limited showing that their product is the "same as" a branded drug. Consistency among generic and name brand manufacturers not only avoids redundant research and monitoring efforts, it also assures consumers and physicians that the generic product is safe and effective.[128]

That difference in initial regulatory burdens marks a stark tension between Hatch-Waxman's quest to quickly and cheaply place generic drugs on the market and a state law tort regime that

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[127] *See, e.g., Greenman v. Yuba Prods., Inc.*, 377 P.2d 897 (Cal. 1963); MATTHEW BENDER 1-6 PRODUCTS LIABILITY PRACTICE GUIDE § 6.03(4)(c).

[128] *Changes in the Labeling of ANDAs Subsequent to Revision of Innovator Labeling* U.S. Department of Health and Human Services, Food and Drug Administration, Division of Generic Drugs, Policy and Procedure Guide 38-89, Aug. 21, 1989.

represents the lone remedy for individuals harmed by inadequate labeling of generic drugs. Nevertheless, Congress did not consider the Hatch-Waxman Amendments in a vacuum, as Actavis would have us do now. Instead, the Amendments serve as just that—amendments—to the FDCA and to the modern regulatory regime governing all prescription drugs that the FDCA first established. Hatch-Waxman's goals are thus tethered to those of the overall regulatory scheme—chief among them the maintenance of safety and efficacy. In this wider context, nothing about the Hatch-Waxman Amendments, and their goal of cheaper drugs, obviates the concomitant prescription that all drugs, even cheaper ones, remain safe. Instead, as Levine explains, "failure-to-warn actions . . . lend force to the FDCA's premise that manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times."[129] "The FDA has limited resources to monitor the 11,000 drugs on the market, and manufacturers have superior access to information about their drugs, especially in the postmarketing phase as new risks emerge."[130] In passing the FDCA, Congress "determined that widely available state rights of action provided appropriate relief for injured [drug] consumers" and that "state-law remedies further consumer protection by motivating manufacturers . . . to give adequate warnings."[131] We see no reason why the same cannot

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[129] *Levine*, 129 S. Ct. at 1202.

[130] *Id.*

[131] Id. at 1199–1200.

be said for the Hatch-Waxman Amendments to the FDCA.

Today's inquiry does not concern the propriety of state failure-to-warn claims. It is enough that such a claim exists; we cannot consider whether a patient—as a policy matter—should have a state-law claim for a drug manufacturer's alleged failure to adequately warn of its products' risks. Louisiana says that she should. We have examined evidence that Congress believed she should not. In this case, unless the law would somehow harness liability onto name brand manufacturers for all failure-to-warn claims, preemption in this case would leave Demahy without a remedy. Yet, "[i]f Congress had intended to deprive [Demahy] of a long available form of compensation, it surely would have expressed that intent more clearly."[132] To hold otherwise would leave us with the bizarre conclusion that Congress intended to implicitly deprive a plaintiff whose doctor prescribes a generic drug of *any* remedy, while under *Levine*, that same plaintiff would have a state-law claim had she only demanded a name brand drug instead.

Our review of the applicable statutes and regulations has not provided evidence sufficient to overcome the presumption against preemption; that is, there is no evidence sufficient for us to say that it was the "clear and manifest purpose" of Congress to preempt state law, or to allow the FDA to do the same.[133] The presumption reflects the judiciary's

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[132] *Bates*, 544 U.S. at 449.

[133] *Levine*, 129 S. Ct. at 1195.

reluctance to find the intention of a coordinate federal branch to supplant state law. The preservation of our federalism requires Congress to do more than it—or the FDA—has chosen to do here. We cannot make the choice for them. The need for supplanting state duties here and the attendant calibration of costs and benefits are far beyond judicial ken—a reality reflected in the legal demands of conflict preemption and not wholly distant from the demands for implications of private rights of action.

Because state imposition of duties to warn on generic drug manufacturers neither renders compliance with federal regulation impossible nor obstructs the goals of that regulation, we AFFIRM the district court's finding that Demahy's state-law failure-to-warn claims are not preempted.

APPENDIX B

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA

JULIE DEMAHY	CIVIL ACTION
VERSUS	NO: 08-3616
WYETH, INC. ET AL.	SECTION: J

ORDER & REASONS

Before the Court is Defendant Actavis Inc.'s ("Actavis") **Motion to Dismiss (Rec. Doc. 19)** under Rule 12(b)(6) based on federal conflict preemption. The motion came before the Court for oral argument on September 17, 2008, and was taken under advisement. Having reviewed the motion, the memoranda of counsel, the parties' statements at oral argument, and the applicable law, the Court finds as follows.

FACTS & PROCEDURAL HISTORY

Plaintiff Julie Demahy ("Demahy"), a fifty-eight year old female, began taking metoclopramide, the generic version of the name brand drug Reglan, in 2002 and continued treatment until April 2006. Metoclopramide is prescribed for treatment of gastroesophagal reflux disease, commonly known as acid reflux. In October of 2007, Demahy was diagnosed by physicians at the University of Texas, Southwestern Medical Center with tardive dyskenesia, which the doctors believed had been caused by long-term use of metoclopramide. Tardive

dyskenesia is a neurological disorder that causes involuntary movements of the face, torso, and extremities.

As a result of her injuries allegedly caused by her treatment with metoclopramide, Demahy filed suit against Wyeth Inc., Schwarz Pharma, Inc., and Actavis in the 22nd Judicial District Court for the Parish of St. Tammany. In her state court complaint, Demahy asserted personal injury claims under the Louisiana Products Liability Act ("LPLA"), specifically for failure to warn of the risks of neurological disorder after long-term use of metoclopramide. In addition, Demahy claims that Actavis breached its duty to provide updated information regarding the hazards of metoclopramide to the Food and Drug Administration ("FDA"), which would have resulted in more adequate warnings on the labels for the drug. Further, Demahy claims that Actavis intentionally concealed scientific research regarding the risks of metoclopramide with respect to neurological disorders in order to mislead the medical community and prevent FDA action.

The case was removed to this Court on June 6, 2008 (Rec. Doc. 1). Defendants Wyeth, Inc. and Schwarz Pharma, Inc. have been dismissed from the suit without prejudice (Rec. Doc. 15). Thus, only defendant Actavis remains. Actavis, formerly Purepak Pharmaceutical Company, is a generic manufacturer of metoclopramide, and according to Demahy's pharmacy records was the manufacturer of the metoclopramide she consumed. The parties do not dispute that Actavis's label and package insert for its generic metoclopramide was at all relevant times

identical to the label and package insert for the name brand drug.

THE PARTIES' ARGUMENTS

Actavis argues that Demahy's products liability claims under the LPLA should be dismissed as a matter of federal conflict preemption. Specifically, Actavis asserts that under the relevant provisions of the Food, Drug, and Cosmetics Act ("FDCA"), the label and package insert for its generic product need not and in fact could not have been altered from the label and package insert that was approved by the FDA for name brand metoclopramide. As such, Actavis argues that Demahy's LPLA failure-to-warn claims are preempted both as a matter of direct conflict preemption, since Actavis's failure-to-warn duties under the LPLA directly conflict with its duties to maintain identical labels under the FDCA, and as a matter of so-called "obstacle preemption," since compliance with failure-to-warn tort principles under the LPLA would frustrate the goals of the FDCA and the 1984 Hatch-Waxman Amendments to the FDCA.

The Hatch-Waxman Amendments provided differing approval standards for generic drug manufacturers from those applicable to name brand drug manufacturers. See 21 U.S.C. § 355(j) (2008). According to Actavis, the Hatch-Waxman Amendment codified FDA regulations in order to streamline generic drug approval and eliminate the need for generic manufacturers to replicate the time-consuming and costly drug safety research already performed by the name brand manufacturer. The

truncated process by which a generic drug is approved is referred to in §355(j) as an Abbreviated New Drug Application ("ANDA") as opposed to the more extensive New Drug Application ("NDA") required for name brand drugs. Under the ANDA process, Actavis asserts that generic drugs are not subject to the same initial and continuing testing and reporting requirements as name brand drugs. Additionally, according to Actavis, the FDA mandates that generic drug labels must always remain identical to the FDA-approved labels of the pioneer name brand drug. See §355(j)(2)(A)(v). As such, Actavis argues that the FDA has specifically rejected the availability to generic drug manufacturers of the Changes Being Effected ("CBE") mechanism provided in 21 C.F.R. §314.70, which allows name-brand drug manufacturers to make unilateral post-approval labeling changes, subject to FDA notice and approval. Accordingly, Actavis asserts that Demahy's LPLA claims are preempted because any state law duty to alter or increase generic drug label warnings over and above the labeling approved by the FDA conflicts with the requirements and goals of the FDCA and applicable regulations.

In opposition, Demahy claims that the §355(j) ANDA labeling requirements apply only during the initial approval process for a generic drug. After a generic drug has been approved by the FDA via the ANDA process, however, Demahy asserts that the generic manufacturer has a continuing duty under the LPLA and the FDCA to include warnings regarding newly discovered risks "as soon as there is reasonable evidence of a causal association with a drug." 21 C.F.R. §§201.57(c)(6)(I) & 201.80(e).

Demahy argues further that while it is "questionable" whether generic manufacturers can utilize the CBE procedures under 21 C.F.R. §314.70 to unilaterally add new safety information to their labels, Actavis still had some duty to at least notify the FDA of possible adverse side effects. Thus, because Actavis essentially did nothing, it should be liable under the LPLA for failure to warn of the adverse neurological side effects of metoclopramide that allegedly caused Demahy's tardive dyskinesia.

In response, Actavis reiterates that generic drug labels must always remain identical to those of the name brand drug. Also, Actavis argues that the regulations relied on by Demahy regarding the duty to update labels are inapplicable to generic drug manufacturers.

LAW & DISCUSSION

As set forth by the Supreme Court in Bell Atlantic Corp. v. Twombly, 127 S. Ct. 1955 (2007), the standard to be applied when deciding a Rule 12(b)(6) motion is not whether it is conceivable that some set of facts could be developed to support the allegations in the complaint, but rather whether the plaintiffs have stated enough facts in the complaint to allow a court to conclude that it is "plausible" that the plaintiffs are entitled to relief. The Court must accept as true all well-plead allegations and resolve all doubts in favor of the plaintiff. Tanglewood East Homeowners v. Charles-Thomas, Inc., 849 F.2d 1568, 1572 (5th Cir. 1988).

As a preliminary matter, it should be noted that Demahy's claims are preempted to the extent

they allege fraud-on-the-FDA under state law with regard to Actavis's alleged intentional concealment of medical research concerning the neurological effects of metoclopramide. See Buckman Co. v. Pl.'s Legal Comm., 531 U.S. 341, 348 (2001) (holding that "state law fraud-on-the-FDA claims conflict with, and are therefore impliedly pre-empted by, federal law"). Therefore, any fraud-on-the-FDA claim by Demahy under Louisiana law is preempted and must be dismissed under Rule 12(b)(6) for failure to state a cause of action.

A. Federal Conflict Preemption

Actavis asserts that Demahy's LPLA failure-to-warn claims are barred as a matter of implied federal conflict preemption[1] under the FDCA and applicable interpretive regulations and other position documents of the FDA.

The principles of implied conflict preemption proceed from the Supremacy Clause of the United States Constitution, and provide that federal law must prevail over state law when "it is **impossible** for a private party to comply with both state and federal requirements or where state law stands as an **obstacle** to the accomplishment and execution of the full purposes and objectives of Congress." Freightliner Corp. v. Myrick, 514 U.S. 280, 287 (1995) (internal quotations and citations omitted) (emphasis

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[1] The parties do not dispute the fact that the FDCA itself does not expressly preempt state law failure to warn claims against generic drug manufacturers. Therefore only implied conflict preemption is at issue.

added). Conflict preemption is "fundamentally a question of congressional intent," as opposed to instances of express preemption in which Congress enacts a statute that expressly provides for preemption of state law. Geier v. Am. Honda Motor Co., 529 U.S. 861, 884 (2000). As such, analysis of implied federal conflict preemption should proceed from a "presumption against pre-emption [sic]" when a case concerns whether state authority conflicts with the existence of federal authority. New York v. F.E.R.C., 535 U.S. 1, 17-18 (2002). Thus when federal authority is at odds with state law, a court must "start with the assumption that the historic police powers of the States," such as health and safety regulation, "were not to be superseded . . . unless that was the clear and manifest purpose of Congress." Hillsborough County, Fl. v. Automative Med. Labs., Inc., 471 U.S. 707, 715 (1985).

B. Agency Interpretations and Judicial Deference

When a court reviews an agency's construction of a statute that it administers, the court must determine "whether Congress has directly spoken to the precise question at issue," for if Congressional intent is clear, both "the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress." Chevron U.S.A., Inc. v. Natural Res. Def. Council, Inc., 467 U.S. 837, 842-43 (1984). However, "if the statute is silent or ambiguous with respect to the specific issue," the court must determine "whether the agency's construction is based on a permissible construction of the statute." Id. at 843. On these terms, agency regulations are

controlling "unless they are arbitrary, capricious, or manifestly contrary to the statute." Id. at 844. Under these broad principles, the Supreme Court has developed three different deference analyses for specific types of agency actions.

1) Chevron Deference

Besides the process of enacting administrative regulations, however, administrative agencies "necessarily make all sorts of interpretive choices, and while not all of those choices bind judges to follow them, they certainly may influence courts facing questions the agencies have already answered." United States v. Mead Corp., 533 U.S. 218, 227 (2001). Nonetheless, "[t]he fair measure of deference to an agency administering its own statute has been understood to vary with the circumstances, and courts have looked to the degree of the agency's care, its consistency, formality, and relative expertness, and to the persuasiveness of the agency's position." Id. at 228 (citations omitted). In this analysis, "the fact that the agency has from time to time changed its interpretation . . . does not . . . lead [to the conclusion] that no deference should be accorded the agency's interpretation of the statute." Chevron, 467 U.S. at 863-64. Additionally, under the Court's holding in Chevron, when Congress has generally conferred authority on an agency, Congress expects the agency to speak with the binding authority of law "when it addresses ambiguity in the statute or fills a space in the enacted law," even if there was no congressional intent for a particular result. Mead Corp., 533 U.S. at 229. In this regard, "[i]t is fair to assume that Congress contemplates

administrative action with the effect of law when it provides for a relatively formal administrative procedure tending to foster the fairness and deliberation that should underlie a pronouncement of such force." Id. Accordingly, most cases in which courts have afforded the high level of Chevron deference to agency statements have involved only the results of notice-and-comment rulemaking, namely regulations, or formal adjudications. Id. at 230. Nonetheless, the Court has occasionally afforded Chevron deference to unofficial agency interpretations depending on the circumstances, but only when the agency's interpretation is "reasonable" and when the authorization and procedure for promulgating the interpretation evidences congressional intent that it be binding. Meade, 533 U.S. at 229-31.

2) Auer Deference

In addition to this high Chevron standard of deference, the Supreme Court has developed a second standard of deference when the language of the regulation is ambiguous. An agency's interpretation of its own ambiguous regulation is entitled to deference unless it is "plainly erroneous or inconsistent with the regulation" being interpreted. Auer v. Robbins, 519 U.S. 452, 461 (1997) (internal quotation marks omitted). As such, the Fifth Circuit employs a two-step test when interpreting an agency regulation: 1) whether the regulation is "ambigu[ous] **with respect to the specific question considered**;" and 2) whether the agency's interpretation of its ambiguous regulation is "plainly erroneous or inconsistent with the regulation." Belt v.

EmCare, Inc., 444 F.3d 403, 408 (5th Cir. 2006) (citing Christensen v. Harris County, 529 U.S. 576, 588,(2000) & Auer, 519 U.S. at 461) (emphasis added).

3) Skidmore Deference

Finally, in addition to Chevron and Auer deference, the Court has developed the third and least deferential Skidmore standard for situations in which an agency lacks the congressional authority required for Chevron deference and the regulation at issue is not ambiguous, thus precluding Auer deference. This Skidmore standard provides that an agency's "rulings, interpretations, and opinions" are not controlling on courts, but merely "constitute a body of experience and informed judgment to which courts and litigants may properly resort for guidance." Skidmore v. Swift & Co., 323 U.S. 134, 140 (1944). As such, an agency's informal position statements are subject to "some weight" and should "make a difference" in a court's preemption analysis. See Geier, 529 U.S. at 883. Nonetheless, the weight of deference under Skidmore is affected by "the thoroughness evident in its consideration, the validity in its reasoning, its consistency with earlier and later pronouncements, and all those factors which give it power to persuade, if lacking power to control." Skidmore, 323 U.S. at 140. Essentially, under Skidmore a court merely considers whether the agency statement at issue has the "power to persuade." Id.

Along with the development of these three differing standards of deference, the Supreme Court has held

that an agency's preemption interpretations of the statutes it is authorized to implement may be entitled to some level of deference. Geier, 529 U.S. at 883 (noting that Department of Transportation's comments supporting the preemptive affect of its Federal Motor Vehicle Safety Standard promulgated under the National Traffic and Motor Vehicle Safety Act should "make a difference" in the Court's conflict preemption analysis). In fact, the Court has held that federal regulations, as well as federal statutes, can themselves preempt state law. Hillsborough, 471 U.S. at 713.

C. The FDA's Position on Preemption of State Law Failure-to-Warn Claims under the FDCA.

Actavis has pointed the Court to five specific pieces of evidence that support its position that the FDCA, applicable regulations, and informal FDA position statements have consistently over the past twenty years supported the proposition that state law failure-to-warn claims based on the inadequacy of generic drug labels are preempted as matter of conflict preemption. Each of these pieces of evidence will be treated in succession.

1) Abbreviated New Drug Application Regulations, 54 Fed Reg 28872, 28884 (proposed July 10, 1989) (hereinafter "1989 Proposed Rule")

The first piece of evidence Actavis cites stems from the proposed rule and comments created during the FDA's initial rulemaking process to implement the provisions of the 1984 Hatch-Waxman

amendments. See 1989 Proposed Rule at 28872 ("[FDA] is proposing regulations to implement [the Hatch-Waxman amendments]"). The proposed rules were intended to "benefit consumers by making generic drug products available more quickly." Id. The relevant portion of the 1989 Proposed Rule cited by Actavis provides the following:

> In addition, the act requires that an applicant include in the ANDA information adequate to show that the proposed labellng [sic] for its drug product is the same as that of the reference listed drug except for changes required because of differences approved under a petition or because the drug product and the reference listed drug are produced or distributed by different manufacturers.. . .
>
> FDA emphasizes that the exceptions to the requirement that a generic drug's labeling be the same as that of the listed drug are limited. The agency will not accept ANDA's for products with significant changes in labeling(such as new warnings or precautions) intended to address newly introduced safety or effectiveness problems not presented by the listed drug. Such labeling changes do not fall within the limited exceptions in sections505(j)(2)(A)(v) and 505(j)(3)(G) of the act. Moreover, FDA does not believe that it would be consistent with the purpose of section 505(j) of the act,

> which is to assure the marketing of generic drugs that are as safe and effective as their brand-name counterparts, to interpret section 505(j)(2)(A)(v) of the act as permitting the marketing of generic drugs with diminished safety or effectiveness and concomitantly heightened labeled warnings. Thus, where a proposed change in a generic drug, e.g., in packaging or inactive ingredients or, for a petition-approved drug, in the approved change, would jeopardize the safe or effective use of the product so as to necessitate the addition of significant new labeled warnings, the proposed product would not satisfy the labeling requirements of sections 505(j)(2)(A)(v) and505(j)(3)(G) of the act.
>
> To assist the agency in determining if the applicant's proposed labeling is the "same as" that of the reference listed drug, except for the types of differences described above, FDA proposes in § 314.94(a)(8)(iv) to require the applicant to include in the ANDA a side-by-side comparison of the applicant's proposed labeling with the currently approved labeling for the listed drug referred to in the ANDA with all differences annotated and explained.

Id. at 28884.

Actavis cites the above quoted portion of the 1989 Proposed Rule for the proposition that "[f]or almost twenty years, the FDA has consistently stated that generic labeling must, **at all times be identical** to name brand labeling and that only it, alone, may determine whether generic labeling should be revised." Def.'s Reply Mem. Supp. Sum. J., 1 (emphasis added). However, the 1989 Proposed Rule does not address the question of whether generic labels must **always** be identical to that of the name brand pioneer drug; rather, the 1989 Proposed Rule concerns **only the initial ANDA application and approval process**, and thus only concerns whether the generic label must be the same as the name brand at the time of the initial ANDA application. See generally 1989 Proposed Rule at 2875-76. Neither party disputes the fact that a generic drug must have the "same" label as the name brand pioneer drug at the time of an initial ANDA application. The crucial question, which the 1989 Proposed Rule does not address, is whether a generic drug *that has already been approved* via the ANDA process can change its label to include new or different warnings without FDA approval. Thus Actavis's reference to the 1989 Proposed Rule merely begs the question at issue in this case of whether a generic drug manufacturer can update its labels to comply with state law tort duties after initial FDA approval without violating the FDCA.

Furthermore, it is interesting to note that from the very beginning, the FDA has required that ANDA applicants include labels that are the "same" as those approved for the name brand pioneer drug. The 1989 Proposed Rule makes numerous references to this

"same as" requirement. On the other hand, the FDA's regulation that specifically applies to *withdrawal* of generic drug approvals after the initial ANDA approval provides that an such approval can be withdrawn if the label for the generic is "no longer **consistent with** that for the listed drug." 21 C.F.R. §314.150(b)(1)(2008). If the FDA truly intended generic drug labels to be the "same as" the name brand drug labels throughout the life of the generic drug, the discrepancy between the manifold use of the phrase "same as" in the FDA's initial rulemaking on the *pre-approval* ANDA process is curious in comparison to the use of the phrase "consistent with" in the regulation governing *post-approval* processes. Further implications of 21 C.F.R. §314.150 with respect to Actavis's preemption arguments are discussed in section C(3) below.

Finally, the 1989 Proposed Rule itself contemplates approval of post-ANDA unilateral labeling changes by generic drug manufacturers. In discussing the different procedural protections that must be afforded to NDA and ANDA approved manufacturers during the approval withdrawal process, the FDA commented:

> The agency recognizes, however, that ANDA holders may been titled to more extensive procedural protections when the agency proposes to withdraw approval of their applications under sections 505(e) of the act rather than under 505(j)(5) of the act. This result is procedurally fair because of the different types of issues to be resolved

> under the two sections of the act. When the agency proposes to withdraw an ANDA under section 505(e)of the act, rather than section 505(j)(5) of the act, **the basis for withdrawal will directly concern aspects of safety and effectiveness, labeling, or manufacturing** that are specific to the ANDA holder's product; the basis for such a withdrawal will not be the safety and effectiveness of the underlying drug substance. **In a 505(e) proceeding that concerns only a specific ANDA and not the underlying drug substance, therefore, the ANDA holder will be in the best position to present relevant evidence and to represent its interests.** In many instances, an ANDA holder alone will possess the information essential to resolving factual issues necessary for the agency to make an informed judgment about whether or not approval of the application should be withdrawn or suspended for grounds specified under section 505(e) of the act.

1989 Proposed Rule at 28904, § N (emphasis added). This portion of the 1989 Proposed Rule references 21 U.S.C. §505(e), which provides various grounds under which the Secretary of the FDA can withdraw an approval of "any drug under [§505]," which would include ANDA approved drugs under §505(j). 21 U.S.C. §505(e)-(j) (2008). One of these grounds specifically applicable to withdrawal of §505(j)

generic ANDA approvals is if "on the basis of new information before him . . . the labeling of such drug. . . is false or misleading." Id. at §505(e). All this taken together suggests that a generic drug manufacturer could in fact unilaterally change its label warnings after initial ANDA approval, subject to the FDA's approval of the change and after due process proceedings on the issue of withdrawal. Therefore, not only does the 1989 Proposed Rule initially beg the question of whether generic manufacturers can make unilateral changes after ANDA approval, it actually answers the question by indicating that generic manufacturers can do so, subject to due process approval or withdrawal by the FDA. As a result, the 1989 Proposed Rule actually undermines Actavis's argument on preemption by indicating that generic manufacturers can make unilateral post-ANDA approval labeling changes.

Finally, this excerpt from §N of the 1989 Proposed Rule sheds light on the meaning of 21 C.F.R. §314.97 (discussed in further detail below in section C(3)). Section 314.97 provides that a generic manufacturer "shall comply with the requirements of [21 C.F.R.] §314.70," which outlines the CBE procedures that include the requirements and process for making unilateral post-approval label changes. See 21 C.F.R. §§314.70(c)(6).[2] Section

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[2] 21 C.F.R. §314.70(c) (6) provides in pertinent part that the holder of an NDA approval may make labeling changes "[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction" when there is evidence of a causal association sufficient to meet the standard for label inclusion under 21 C.F.R. §201.57(c). 21 C.F.R. §314.70(c) (6) (iii) (A) (2008). The

314.97 was first proposed in the 1989 Proposed Rule; additionally, in the FDA report regarding the final rulemaking process for 21 C.F.R. §314, the FDA notes that they "received no comments on [§314.97] and . . . finalized it without change." Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17950, 17965 (Apr. 28, 1992). Thus throughout the entire life of the regulations governing generic drug labeling changes, §314.97 has mandated, without any opposition or comment, that generic manufacturers "shall comply" with the CBE labeling change provisions of §314.70(c)(6). As a result, generic manufacturers should be able to unilaterally change their labels after initial ANDA approval, albeit subject to FDA oversight and approval under §314.70(c)(6).

Under the above analysis, the appropriate level of deference that this Court should give the 1989 Proposed Rule is essentially irrelevant, because the 1989 Proposed Rule does not shed any pertinent light on the issue of whether the FDCA preempts

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current language of this provision went into effect on September 22, 2008. The reference to the §201.57(c) evidentiary standard requires that warnings be based on "clinical data" or possibly" serious animal toxicity." 21 C.F.R. §201.57(c). Thus, the reference to §201.57(c) in §314.70(c) (6) (iii) (A) ensures that any added warnings will be sufficiently substantiated to merit inclusion on the label.

The prior version of §314.70(c) (6) (iii) (A), which would have been in effect during the period relevant to this case, provided essentially the same CBE procedure for labeling changes, but without reference to "evidence of a causal association" under §201.57(c). Regardless, the differences between the current and former versions of §314.70(c) (6) (iii) (A) are irrelevant to this analysis. See 21 C.F.R. §314.70(c) (6) (iii) (A) (2007).

Demahy's failure-to-warn claims under the LPLA. Furthermore, to the extent that the 1989 Proposed Rule is relevant at all to the issue of preemption, it actually contemplates unilateral labeling changes by generic manufacturers, and thus goes against a finding of preemption as argued by Actavis.

2) Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17950 (Apr. 28, 1992) (hereinafter "1992 Final Rule")

The next pieces of evidence cited by Actavis in support of its preemption argument are FDA comments on the final rule that enacted the federal regulations promulgated under the Hatch-Waxman amendments and which govern the ANDA application process. See 1992 Final Rule, at 17950 ("These regulations implement title I of the [Hatch-Waxman Amendments]. This final rule covers subjects such as ANDA content and format, approval and nonapproval of an application, and suitability petitions.").

Again, as with Actavis's reference to the 1989 Proposed Rule, the 1992 Final Rule specifically deals only with labeling requirements for generic manufacturers who are in the initial ANDA application process, and does not address post-approval labeling changes. See, e.g., 1992 Final Rule, at 17951-52. Nonetheless, Actavis cites the 1992 Final Rule for the proposition that generic labels must always be the same as name brand labels throughout the life of the generic drug. However, the section of the 1992 Final Rule that Actavis cites is the FDA's response to a public comment on 21 C.F.R.

§314.1, which lays out the scope of §314, suggesting that the "FDA accept ANDA's with warnings or precautions in addition to those" on the name brand pioneer drug's label. Id. at 17953. The FDA disagreed with the comment and stated that "the applicant's proposed labeling" for a generic ANDA must be the "same as" that of the listed name brand drug. Id. Thus, as with the 1989 Proposed Rule, the comment relates only to "applicants," not manufacturers who have already received ANDA approval, and uses the "same as" language, which is crucially different from the "consistent with" language of §314.150(b)(1). In fact, the 1992 Final Rule expressly distinguishes between ANDA "**applicants**," the manufacturers seeking ANDA approval, and ANDA "**holders**," those who have received approval. See, e.g., 1992 Final Rule at 17951 ("The final rule is substantially similar to the proposal, although FDA has made some minor changes, such as requiring **applicants** to include a table of contents in the review copies of an ANDA . . . and other minor changes regarding periodic reports from ANDA **holders**.") (emphasis added).

Further, Actavis specifically cites Comment 20 of the 1992 Final Rule, which includes the FDA's response to a public comment suggesting that generic manufacturers be allowed to submit a suitability petition[3] for an ANDA "for a product whose labeling differs from the [name brand] drug by being 'more

[3] A suitability petition is the mechanism by which a manufacturer may seek approval for "drugs that have a different active ingredient, route of administration, dosage form, or strength." 1992 Final Rule, at 17957.

clear or offer[ing] better directions regarding how the drug should be taken." Id. at 17957, Cmt. 20. The FDA first noted that "[l]abeling differences . . . are not proper subjects for a suitability petition," then went on to "remind[] applicants that the labeling for an ANDA product must be the same as the labeling for the [name brand] product." Id. The comment also notes that an ANDA applicant who believes that the labeling for a proposed drug product should differ from that of the name brand drug should contact the FDA for a determination of whether both the generic and name brand labels should be changed. Id. Again, this section refers only to ANDA "applicants," and not to generic manufacturers who have already obtained ANDA approval.

The 1992 Final Rule does include the FDA's first suggestion that a generic manufacturer cannot make post-approval label changes without prior FDA approval. In response to a public comment suggesting that the FDA allow ANDA applicants to deviate from the name brand label to add safety-related information, the FDA suggested that "[a]fter approval of an ANDA, if an ANDA holder believes that new safety information should be added, it **should provide** adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised." Id. at 17961, cmt. 40 (emphasis added). While this suggestion supports Actavis's position that generic manufacturers cannot change their labels without prior FDA approval, the comment cannot be taken at face value. First, it should be noted that the comment is in response to a suggestion that *applicants* be allowed to deviate from the name brand label. Thus,

to the extent that the FDA's response suggests that ANDA *holders* must receive FDA approval before making label changes, the response is outside the public comment's scope. Second, this non-responsive comment by the FDA flies in the face of 21 C.F.R. §314.97, which as noted above mandates that generic manufacturers shall comply with the provisions of 21 C.F.R. §314.70, the regulation that establishes the CBE procedures. Finally, Comment 40 does not expressly preclude generic manufacturers from making unilateral label changes; it merely suggests that they "should provide" relevant information to the FDA. This permissive language in a non-responsive comment does not constitute a definitive statement by the FDA that generic manufacturers cannot unilaterally update their labels. Thus not only is this non-responsive, and merely permissive, comment extraneous, it is also inconsistent with §§314.97 and 314.70. As a result, Comment 40 is either irrelevant or merely entitled to Skidmore deference, and does not have the power to persuade in support of Actavis's preemption position.

Finally, as it did in the 1989 Proposed Rule, the FDA suggests in the 1992 Final Rule that generic manufacturers *can unilaterally change their labels* without prior FDA approval. In response to a comment suggesting that NDA and ANDA holders should submit the same post-marketing reports on their products, the FDA stated:

> After careful consideration, FDA has revised § 314.98 [the post-marketing reporting provision] to require ANDA applicants to submit a periodic report of

> adverse drug experiences even if the ANDA applicant has not received any adverse drug experience reports **or initiated any labeling changes**. As revised, the requirement is identical to that imposed on NDA holders. **Periodic reports by ANDA holders will help FDA determine whether ANDA products have appropriate labeling** and ensure that no adverse drug experiences go unreported.

1992 Final Rule, 17965, cmt. 53. This comment, in the context of post-marketing reporting requirements, clearly contemplates that a generic manufacturer with ANDA approval may initiate labeling changes. Furthermore, the comment anticipates such unilateral labeling changes by ANDA holders because it notes that post-marketing reporting requirements "will help FDA determine whether ANDA products have appropriate labeling," which suggests that labels may have been changed by ANDA holders after initial approval. Therefore, as in the 1989 Proposed Rule, the FDA expressly contemplates unilateral label changes by generic manufacturers with ANDA approvals. As such, the 1992 Final Rule does not support Actavis's preemption position.

Again, as with the 1989 Proposed Rule, the level of deference this Court should give the 1992 Final Rule is irrelevant since the 1992 Final Rule does not speak directly to the issue of preemption. The only suggestion of preemption in the 1992 Final Rule is couched in permissive terms, and is then

undermined by the FDA's later recognition of the possibility of unilateral label changes by generic manufacturers.

Nonetheless, the 1989 Proposed Rule and the 1992 Final Rule, to the extent that they are relevant, are entitled to the high level of Chevron deference afforded agency decisions made pursuant to notice-and-comment rulemaking. However, in contrast to Actavis's arguments, the relevant portions of the 1989 Proposed Rule and 1992 Final Rule reveal that the *FDA took no direct position* on this issue of preemption in those notice-and-comment produced statements, and even suggested the possibility of unilateral labeling changes by generic manufacturers. In fact, only very recently (see section C(4) below) has the FDA directly addressed whether generic manufacturers can unilaterally alter their labels with respect to preemption of state law failure-to-warn claims. As such, the FDA's position on preemption of state law failure-to-warn claims against generic manufacturers *has not been consistent* over the last twenty years. Moreover, the only relevant portions of the 1989 Proposed Rule and the 1992 Final Rule that are subject to Chevron deference actually suggest that the FDA *historically confirmed* the right of generic manufacturers to unilaterally alter their labels. This conclusion is bolstered by the fact that the FDCA does not expressly preempt state law products liability claims, and the fact that such claims come under the traditional and presumptively non-preempted power of the states to protect the health and safety of their citizens.

Furthermore, to the extent the 1989 Proposed Rule and the 1992 Final Rule can be construed as FDA interpretations of their ambiguous regulations on the exact issue of preemption, they would be subject to Auer deference. However, because the rules are inconsistent with other FDA statements and regulations, they are not entitled to Auer deference. As such, they are entitled to Skidmore deference only, and they do not have the power to persuade under that standard.

3) **21 C.F.R. §314.150**

The third piece of evidence allegedly supporting Actavis's arguments regarding conflict preemption is 21 C.F.R. §314.150, which has already been discussed to some extent above. Section 314.150 establishes the grounds under which the FDA can withdraw approval of an NDA or ANDA. 21 C.F.R. §314.150 (2008). Actavis cites §314.150 for the proposition that generic drugs must always follow the labeling of the name brand drug "verbatim" even after initial approval of the generic product via the ANDA process.

However, as discussed above, §314.150 does not use the word "verbatim" or the phrase "same as" in its provisions applicable to withdrawal of an ANDA based on labeling changes. The text of §314.150 provides in pertinent part that the FDA may withdraw an ANDA if "the labeling for the drug product that is the subject of the abbreviated new drug application **is no longer consistent with** that for the listed drug referred to in the abbreviated new drug application, except for differences approved in

the [ANDA]." Id. Again, as noted above, the term "no longer consistent with" does not mean "verbatim," "identical," or "same as." A generic label may be "consistent with" a name brand label even if it is not exactly the "same as" that label. Further, even if the generic label includes additional warnings that do not appear on the name brand label, these additional warnings may still be "consistent with" the general purpose of the name brand label to inform the consumer of the relevant risks of the drug. Regardless, the conspicuous use of the phrase "consistent with" as opposed to the phrase "same as" which appears in the FDA's regulatory comments, and the term "verbatim" which appears in Actavis's pleadings, suggests that generic labels may not necessarily have to be exactly the same as name brand labels throughout the life of the generic product. Thus, §314.150 does not expressly prohibit generic manufacturers from making unilateral labeling changes under the CBE process, and therefore does not support Actavis's preemption argument.

4) Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed Reg 2848, 2849-2850 (proposed January 16,2008) (hereinafter "2008 Proposed Rule").

The next evidence Actavis relies on are the FDA's comments in a recent proposed rule concerning amendments to the regulations governing supplemental applications for proposed labeling changes for approved drugs. 2008 Proposed Rule, at

2848. The 2008 Proposed Rule is intended to update and codify the FDA's allegedly "longstanding view" on when labeling changes can be made without prior FDA approval via the CBE process. The 2008 Proposed Rule includes the first and only explicit notice-and-comment produced statement by the FDA that generic drug manufacturers cannot utilize the CBE label change procedure under 21 C.F.R. §314.70(c)(6)(iii)(A):

> **FN1 CBE changes are not available for generic drugs approved under an [ANDA] under 21 U.S.C. 355(j).** To the contrary, a generic drug manufacturer is required to conform to the approved labeling for the listed drug. See 21 CFR 314.150(b)(10); see also 57 FR 17950, 17953, and17961.

2008 Proposed Rule, at 2849, n.1 (emphasis added).

It should first be noted that the 2008 Proposed Rule's main purpose is to propose changes to the mechanics of the §314.70 CBE procedures. As a result, the 2008 Proposed Rule has *nothing whatsoever to do* with the existence or availability of those procedures to ANDA holders. Furthermore, while the FDA does expressly indicate that the CBE procedure is not available to generic drug manufacturers with ANDA approval, this comment is relegated to a mere *footnote* in the *Supplementary Section* of a *proposed* rule that *does not mention ANDA or generic manufacturers anywhere else in the entirety of the proposed rule*. The FDA essentially took the opportunity to make a significant statement

on preemption of generic drug labeling claims in the relative obscurity of a footnote in the introductory statement of a document that has nothing at all to do with rules pertaining to generic drugs or to the ANDA process. The Fifth Circuit has suggested that a footnote to a finalized regulation, even though it may have been the product of notice-and-comment rulemaking, may not be entitled to Chevron or Auer deference. See Langbecker v. Elec. Data Systems Corp., 476 F.3d 299, 311 n.22 (5th Cir. 2007). As such, a footnote in a proposed rule should not be afforded any significant level of deference.

Additionally, this statement in a footnote in the 2008 Proposed Rule *contradicts the FDA's own regulations*. As noted above, 21 C.F.R. §314.97 provides in full: "[an ANDA applicant] shall comply with the requirements of §§ 314.70 and 314.71 regarding the submission of supplemental applications and other changes to an approved abbreviated application." 21 C.F.R. §314.97 (2008). Thus because §314.70(c)(6)(iii)(A) explicitly allows for unilateral labeling changes, and since §314.97 explicitly mandates that ANDA applicants and holders "shall comply" with §314.70, the FDA's statement that generic manufacturers with ANDA approval cannot utilize CBE labeling changes *directly contradicts the FDA's own regulations*.

Finally, and perhaps most importantly, even if the FDA's footnoted statement in the 2008 Proposed Rule were not extraneous and contradictory, it is entitled to no deference whatsoever under Fifth Circuit precedent. In no uncertain terms, the Fifth Circuit has held that "proposed regulations are

entitled to no deference until final." In Re Appletree Markets, Inc., 19 F.3d 969, 973 (5th Cir. 1994). Therefore, not only is the statement that generic manufacturers cannot make CBE labeling changes irrelevant in its own context and contradictory to the FDA's own regulations, it is not entitled to any deference at all under Fifth Circuit law. Therefore, the 2008 Proposed Rule does nothing to support Actavis's position.

a) Cases Applying the Non-Preemption Analysis

Further, and consistent with the above analysis, the District Court for the Western District of Washington has held that generic drug manufacturers have the same ability as name brand manufacturers to unilaterally update their labels via the CBE provisions of §314.70. Laisure-Radke v. Par Pharm., Inc, 2006 WL 901657 (W.D. Wash. 2006). The Laisure-Radke court was faced with the same issue currently before this Court, namely whether there was a conflict between Washington state law failure-to-warn claims based on generic drug labels and the FDCA. Id. at *3. The defendant generic drug manufacturer in Laisure-Radke argued that under the Hatch-Waxman Amendments to the FDCA and 21 C.F.R. §314.94, which requires ANDA applicants to submit side-by-side comparisons of the approved name brand and proposed generic labels, "a generic manufacturer simply cannot deviate its labeling from that of the [name brand] drug." Id. The court noted that generic and name brand labels must indeed be identical during the initial ANDA approval process, but found that "*once the ANDA is approved*, generic

manufacturers have the same power and duty to add or strengthen their warnings, as do the manufacturers of pioneer drugs, and therefore the same liability." Id. (emphasis in original). The Laisure-Radke court relied on the Fourth Circuit's 1994 decision in Foster v. American Home Products Corp., which reviewed the issue of whether a name brand manufacturer can be held liable for negligent misrepresentation caused by another company's generic product. Id. (citing Foster, 29 F.3d 165 (4th Cir. 1994). The Foster court held that under 21 C.F.R. §§314.70 and 314.97, generic manufacturers have the same ability to alter a generic drug's labeling to strengthen or add warnings as name brand manufacturers. Id. at *4 (citing Foster, 29 F.3d at 169). Although the Foster court addressed a different legal issue, the Laisure-Radke court found its reasoning persuasive. As such, the Laisure-Radke court held that under §314.70, which expressly applies to generic drug manufacturers under §314.97, "once a generic drug manufacturer holds an approved ANDA for a particular product, it can add or strengthen a contraindication, warning, precaution or adverse reaction at any time without prior FDA approval." Id. at *5.

It should be noted that the Laisure-Radke decision was handed down in 2006, before the FDA's footnoted statement in the 2008 Proposed Rule that generic manufacturers cannot utilize the CBE process to make unilateral label changes. However, as discussed above, the statement in the 2008 Proposed Rule is contradictory and extraneous, and also commands no deference from a Fifth Circuit court.

Further, several cases have agreed with the Foster/Laisure-Radke analysis even after the advent of the 2008 Proposed Rule. Like the Foster case, these cases arose in the context of claims against name brand manufacturers for failure to update their own labels, which in turn rendered the labels of generic drugs inadequate. Thus, these cases essentially involved claims against name brand manufacturers for faulty labeling on generic drugs that the name brand manufacturers did not even produce. See, e.g., Swicegood v. Pliva, Inc., 543 F. Supp. 2d 1351, 1358 (N.D. Ga. 2008); Morris v. Wyeth, 2008 WL 2677048, *3 (W.D. Ky. 2008); Smith v. Wyeth, Inc., 2008 WL 2677051, *3 (W.D. Ky. 2008); Wilson v. Wyeth, Inc., 2008 WL 2677049, *3 (W.D. Ky. 2008).[4] Due

to the posture of these cases, the issue of preemption was not raised by the parties, and as such the courts either expressly avoided the preemption issue, or spoke on the issue in dicta only. See, e.g. Swicegood, 543 F. Supp. 2d at 1358 n.1 (noting that defendants did not argue for dismissal based on federal statutory preemption, but also noting that Georgia courts have held that state common law claims are not preempted by the FDCA). Nonetheless, all these cases rely to some degree or another on the policy arguments presented in Foster:

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[4] The cases from the Western District of Kentucky were apparently all related as the decisions employ virtually identical language and all deal with issues of liability for generic labeling of metoclopramide.

We do not accept the assertion that a generic manufacturer is not responsible for negligent misrepresentations on its product labels if it did not initially formulate the warnings and representations itself. When a generic manufacturer adopts a name brand manufacturer's warnings and representations without independent investigation, it does so at the risk that such warnings and representations may be flawed. In cases involving products alleged to be defective due to inadequate warnings, the manufacturer is held to the knowledge and skill of an expert . . . . The manufacturer's status as expert means that at a minimum he must keep abreast of scientific knowledge, discoveries, and advances and is presumed to know what is imparted thereby. The same principle applies in the instant case; as an expert, a manufacturer of generic products is responsible for the accuracy of labels placed on its products. Although generic manufacturers must include the same labeling information as the equivalent name brand drug, they are also permitted to add or strengthen warnings and delete misleading statements on labels, even without prior FDA approval. 21 C.F.R.§314.70 (1993). The statutory scheme governing premarketing approval for drugs simply does not evidence Congressional intent

> to insulate generic drug manufacturers from liability for misrepresentations made regarding their products, or to otherwise alter state products liability law. **Manufacturers of generic drugs, like all other manufacturers, are responsible for there presentations they make regarding their products.**

Foster, 29 F.3d at 169-70 (internal quotations and citations omitted) (emphasis added). In the context of the above language from Foster, the Swicegood court held that "Defendant [generic manufacturer] had the ability - albeit with approval from the FDA -to add to or strengthen a contraindication, warning, precaution, or adverse reaction." 543 F. Supp. 2d at 1358 (citing 21 C.F.R. §314.70 and Colacicco v. Apotex, Inc., 432 F. Supp. 2d 514, 523 (E.D. Pa. 2006)). Also, the Morris/Smith/ Wilson cases held that "FDA regulations allow the manufacturer of a generic drug "[t]o add or strengthen a contraindication, warning, precaution or adverse reaction . . . without prior FDA approval." Morris, 2008 WL 2677048 at *4; Smith, 2008 WL 2677051 at *4; Wilson, 2008 WL 2677049 at *4. While these courts did not squarely address the issue of preemption, they relied on the Foster/Laisure-Radke policy analysis, which is itself supported by the interplay between §§314.70 and 314.97. Thus these cases support the proposition that state law failure-to-warn claims are not preempted by the Hatch-Waxman Amendments or the relevant FDA statements on preemption.

Finally, the California Court of Appeal has recently held that the FDCA does not preempt state-law failure-to-warn claims. McKenney v. Purepac Pharm. Co., 83 Cal. Rptr. 3d, 810 (Cal. App. 5th Dist. Sept. 25, 2008). The McKenney case involved the same defendant[5] as in this case and the same failure-to-warn claims under California law based on the absence of a tardive dyskenesia warning on the label for generic metoclopramide. Id. at 813. Citing the 1992 Final Rule for support, the McKenney court found "no reason to distinguish between original or [name brand] drugs and their generic equivalents for federal preemption purposes." Id. at 818. Thus, the McKenney court correctly noted that the 1992 Final Rule actually takes a *non-preemption* position, and properly concluded that the FDA's conflicting statements do not support preemption.

Actavis has cited several other post-2008 Proposed Rule decisions that have found preemption of state law failure-to-warn claims for inadequate generic drug labeling based on the FDA's statement in the proposed rule. See Mensing v. Wyeth, ---- F. Supp. 2d ----, 2008 WL 2444689, * 8 (W.D. Minn. 2008); Gaeta v. Perrigo Pharmaceuticals Co., 2008 WL 2548813, *4 (N.D. Cal. 2008); Bolin v. Smithkline Beecham Corp., 2008 WL 3286973, *8 (S.D. Fla. 2008); Masterson v. Apotex Corp., 2008 WL 3262690, *4 (S.D. Fla. 2008); Valerio v. Smithkline Beecham Corp., 2008 WL 3286976, *8 (S.D. Fla. 2008). However, none of these cases address the apparent contradiction between the FDA's statement in the

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[5] As noted above, Actavis was formerly Purepac Pharmaceutical Company.

2008 Proposed Rule and the clear mandate of §314.97 that generic manufacturers "shall comply" with the requirements of §314.70. As such, the analysis of the Foster/Laisure-Radke cases is more persuasive, since that analysis takes into account the contradiction between the footnoted language of the 2008 Proposed Rule and the binding mandate of §§314.97 and 314.70.

Additionally, none of the cases cited by Actavis distinguish between the "consistent with" language of §314.150, which is the regulation that Actavis and most other generic manufacturers have relied on for the proposition that generic labels must always be the "same as" name brand labels, and the "same as" language used in the FDA's comments on the regulation during the proposal and final rulemaking processes (in the 1989 Proposed Rule and the 1992 Final Rule).

Finally, none of these cases address the fact that the 1989 Proposed Rule and the 1992 Final Rule actually suggest a non-preemption position, as noted by the McKenney court. Accordingly, these cases are not persuasive.

b) The Mensing Decision

The case cited by Actavis that most directly supports the FDA and Actavis's preemption position is Mensing v. Wyeth, which was expressly adopted by the other 2008 cases from the Southern District of Florida that Actavis has cited. ---- F. Supp. 2d ----, 2008 WL 2444689 (W.D. Minn.); see also Bolin v. Smithkline Beecham Corp., 2008 WL 3286973, 8 (S.D. Fla. 2008). As such, a close reading and

criticism of the Mensing decision will bolster the non-preemption analysis.

Mensing involved the exact same claims that Demahy has brought before this Court, namely that generic metoclopramide manufacturer Actavis negligently failed to include warnings of the risk of tardive dyskinesia on its labels in violation of state law failure-to-warn duties. 2008 WL 3286973 at *1. Specifically, the Mensing plaintiff argued that "Actavis . . . ignored scientific and medical literature establishing a higher risk of developing tardive dyskinesia, failed to request a labeling revision to the FDA, and failed to report safety information directly to the medical community." Id. In opposition, Actavis argued that plaintiff's claims were conflict preempted. Id. In response to the preemption argument, plaintiff asserted that while generic manufacturers may be required to submit identical labels to that of the name brand drug during the *initial* ANDA approval process, they nonetheless have a duty to update their labels post-ANDA approval to include newly discovered warnings. Id.

The Mensing court initially considered the pertinent provisions of the FDCA, the legislative history of the act, the governing regulations, and the FDA's comments on the regulations to conclude that a generic manufacturer cannot unilaterally alter its labels. Id. at *5. In support of its finding of preemption, the Mensing court initially cited the 1989 Proposed Rule in holding that "the FDA's own comments in implementing the Hatch-Waxman Act support the conclusion that a generic manufacturer is not free to unilaterally alter the labeling from that of

the name brand drug." Id. However, as noted in the above discussion, the 1989 Proposed Rule was concerned only with pre-ANDA approval requirements, not post-ANDA approval duties. Also, the 1989 Proposed Rule itself goes on to suggest that generic manufacturers can unilaterally change their labels post-ANDA approval, subject to FDA approval. See 1989 Proposed Rule at 28904, § N (discussed above at section C(1)).

Next, the Mensing court cited §314.150 and the portions of the 1992 Final Rule discussed in section C(2) above to support its finding of preemption. Mensing, 2008 WL 2444689 at * 5-6. Specifically, the Mensing court noted that §314.150 allows for withdrawal of an ANDA if a generic label is no longer "consistent with" the name brand label, and quoted the 1992 Final Rule comment that "[a]fter approval of an ANDA, if an ANDA holder believes that new safety information should be added, it should provide adequate supporting information to FDA" for the FDA to determine whether a label change is appropriate. Id. However, the Mensing court did not discuss the significant difference between the "consistent with" language of §314.150 and the "same as" language used throughout the FDA's 1989 Proposed Rule and 1992 Final Rule. Also, the Mensing court did not point out that the "should provide" language of the 1992 Rule is simply permissive and not mandatory, whereas the language of §314.97 is mandatory. Finally, the Mensing court ignored other statements by the FDA in the 1992 Final Rule that suggest that generic manufacturers can unilaterally alter their labels.

The Mensing court also disagreed with plaintiff's argument that the CBE mechanism provided in §314.70 allows generic drug manufacturers to make unilateral label changes. Relying on an FDA amicus brief, the Mensing court pointed out the FDA's argument that:

> Although [21 C.F.R. §314.97] contains a provision requiring [ANDA] applicants to 'comply with the requirements of §314.70 . . .' *that provision does not modify the requirement that the drug label for a generic drug must be the* ***same as*** *the label for the approved innovator drug . . . Any ambiguity in the regulatory text has been clarified by FDA, which explained at the time of the promulgation that the regulations do not authorize drug manufacturers to add new warnings to the approved labeling for the innovator drug.* **See** 57 Fed. Reg. at17961, 17953, 17955.

Mensing, 2008 WL 2444689 at *7 (emphasis in original).

Although the Mensing court may have been entitled to rely on the FDA's amicus position regarding the ambiguity between §314.97 and §314.70, this Court is not required to give full deference to the FDA's statements in an amicus brief. See Belt v. EmCare, Inc., 444 F.3d 403, 416 n.35 (5th Cir. 2006) (noting that Auer deference, not Chevron deference, is appropriate for informal agency interpretations "such as . . . *amicus curiae* briefs").

Furthermore, Auer deference is only appropriate if the regulation being interpreted is actually ambiguous; otherwise, only Skidmore deference is necessary. Moore v. Hannon Food Service, Inc., 317 F.3d 489, 494-95 (5th Cir. 2003). Although the FDA claimed in Mensing that it had "clarified" any "ambiguity" in the regulations with respect to the provisions of §314.97, the provisions of that regulation are simple, concise, and patently unambiguous. Therefore, only Skidmore deference is necessary. Accordingly, because the FDA position in Mensing cited only the 1992 Final Rule, with all its internal inconsistencies and irrelevancies, to support its position that it has clarified any ambiguities with regard to §314.97, this Court need not give that position any deference since it does not have the "power to persuade" under Skidmore. Furthermore, the FDA position cited in Mensing makes the assertion that a generic drug label must always be the "same as" the name brand label, without citing to any definitive source for that assertion. This may be due to the fact that there is *no definitive regulation* that dictates that generic drug labels must *always* be the "same as" the corresponding name brand label. As a result, the FDA's position that generic labels must always be the "same as" the name brand label is also not entitled to Auer deference because that position is inconsistent with the regulations at issue. As such, only Skidmore deference applies, and since the FDA's position cannot persuade, it should receive no deference.

Finally, the Mensing court relied on the FDA's footnote in the supplementary introduction to the 2008 Proposed Rule indicating that generic

manufacturers cannot unilaterally change their labels. Mensing, 2008 WL 2444689, *8. As discussed above, Fifth Circuit courts need not give any deference to an agency's statements in proposed rules. Additionally, the FDA's footnote in the 2008 Final Rule is extraneous to the purpose of the proposed rule and is contradictory to the FDA's own regulation in §314.97. As such, the Mensing court's analysis is not persuasive in this matter.

5) Colacicco v. Apotex, Inc.- 432 F. Supp. 2d 514, 528-29 (E.D. Penn. 2006) (aff'd 521 F.3d 253 (3d Cir. 2008)

The final piece of evidence Actavis presented to this Court in support of its preemption position was the Eastern District of Pennsylvania's decision in Colacicco v. Apotex, Inc., which determined that the FDCA preempts state law failure-to-warn claims against generic drug manufacturers. It should first be noted that the Third Circuit in affirming the Colacicco district court's decision expressly left open the question of "whether actions against generic drug manufacturers are preempted on the basis of their obligations under the Hatch-Waxman Amendments [and limited its holding] to circumstances in which the FDA has publicly rejected the need for a warning that plaintiffs argue state law requires." Colacicco v. Apotex, Inc.,521 F.3d 253, 271-272 (3d Cir. 2008). There is no allegation or record evidence in the instant case regarding whether the FDA considered and rejected a neurological risk warning for generic metoclopramide. As such, the Third Circuit's decision has no relevance to the specific issue before this Court, namely whether claims against a generic

manufacturer are preempted under the Hatch-Waxman Amendments in circumstances in which the FDA *has not publicly rejected* a proposed warning. Therefore, Actavis's assertion that the Third Circuit in Colacicco agreed with the "FDA's longstanding position . . . that a plaintiff's state law failure to warn claims asserted against a generic drug manufacturer are conflict-preempted as a matter of law" is patently erroneous. Def.'s Reply Memo Opp. Summ. J., 1.

Nonetheless, Actavis points this Court to the Colacicco district court's opinion on the issue of preemption of state law failure-to-warn claims against generic manufacturers. Colacicco was fundamentally different from this case in that it involved Pennsylvania state law claims against both name brand and generic manufacturers for failure to warn of the increased risk of suicide caused by certain anti-depressant medications. Colacicco v. Apotex, Inc., 432 F. Supp. 2d 514, 520 (E.D. Pa. 2006). As such, the Colacicco district court's opinion addressed FDA preemption statements with respect to claims against both name brand and generic manufacturers. After a lengthy discussion of the proper level of deference that should be given to FDA position statements on the issue of preemption, the Colacicco district court determined that it should give deference to the government's amicus briefs filed in the case as well as the FDA's 2006 Preemption Preamble.[6] Id. at 524-25. In response to the plaintiff's

[6] The so-called "Preemption Preamble" is the FDA statement that initiated the FDA's broad position regarding preemption of state law failure to warn claims under the FDCA. See 71 Fed. Reg. 3922-01, 3933-3936, part D. Comments on Product Liability Implications of the Proposed Rule (Jan. 24,

specific argument that the §314.70 CBE procedure allows generic drug manufacturers to unilaterally update their labels, the Colacicco district court held that "principles of deference do not allow us to question the FDA's interpretation of its own regulations - e.g. that generic drug manufacturers can not (sic) make changes without prior approval." Id. at 528. The Colacicco district court therefore relied solely on the text of §§314.70 and 314.150, as well as statements by the FDA in the 1992 Final Rule (discussed above in section C(2)) as a basis for its "deference" to the FDA's position on preemption.

2006). The Preemption Preamble generally and broadly states the FDA's position that it alone has authority to make the final decision regarding the safety and labeling of prescription drugs, and therefore state law products liability claims against prescription drug manufacturers should be preempted. However, because the Preemption Preamble does not deal specifically with claims against *generic* drug manufacturers, its relevance to the instant case is minimal.

Furthermore, this final preamble section to the rulemaking comments was not subject to the strictures of the rulemaking process, and in fact "*conflict[s]* with statements made in the original notice of proposed rulemaking out of which the 2006 Final Rule grew" See In Re Vioxx, 501 F. Supp.2d 776, 787 (E.D. La. 2007) (emphasis added). In fact, the initial proposed rulemaking notice actually expressly stated that "this proposed rule does not preempt State law . . . [nor] contain policies that have federalism implications or that preempt state law." Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels, 65 Fed. Reg. 81082, 81103 (Dec. 22, 2002). Accordingly, and despite Actavis's argument to the contrary, only Skidmore deference would be appropriate in the context of the Preemption Preamble. As such, to the extent it is at all relevant to this case, it does not have the power to persuade.

Prominently absent from the Colacicco district court's analysis is any discussion of §314.97, the regulation that specifically mandates generic manufacturers to comply with the provisions of §314.70. Furthermore, as noted numerous times in this discussion, the FDA's comments in the 1992 Final Rule regarding whether generic manufacturers can unilaterally update their labels are not entitled to deference because they are inconsistent and ambiguous.

Therefore, because the Colacicco district court decision involved crucially different facts as well as a deference position that is inconsistent with the views of this Court's analysis, this Court does not afford the Colacicco district court's decision persuasive weight in this matter.

6) Summary

In sum, none of the evidence cited by Actavis in this case is dispositive on the issue of whether Demahy's LPLA failure-to-warn claims are preempted under the FDCA and the applicable regulations and FDA statements. The 1989 Proposed Rule and 1992 Final Rule are generally entitled to Chevron deference, but since those documents do not answer the discrete question before this court, they are irrelevant regardless of the appropriate level of deference. Further, to the extant they are relevant, the 1989 Proposed Rule and the 1992 Final Rule actually contemplate unilateral labeling changes by generic drug manufacturers. Also, to the extent that those statements interpret ambiguous FDA regulations as precluding unilateral label changes by

generic manufacturers, they would merit Auer deference. However, because they are inconsistent with the unambiguous language of §314.97 and §314.70 and are thus unreasonable, they are only entitled to Skidmore deference and do not have the power to persuade.

Additionally, the FDA's interpretations of §314.150 are entitled only to Skidmore deference since those interpretations are not consistent with other regulations, namely §314.70 and §314.97, nor are they consistent with other FDA statements on the issue of labeling changes. Thus, these statements should not receive Auer deference, as they are inconsistent with valid regulations, and do not have the power to persuade as a matter of Skidmore deference because they are inconsistent and contradictory.

Furthermore, the 2008 Proposed Rule is not entitled to any deference in this Court, and the cases relying on that rule are inapposite and unpersuasive.

Finally, the Colacicco case involved crucially different facts in that the proposed warning at issue in that case had *been expressly rejected by the FDA.*

As such, this Court finds that Demahy's failure-to-warn claims under the LPLA are not preempted as a matter of conflict preemption under the FDCA, applicable regulations, and relevant FDA position statements. Accordingly,

IT IS ORDERED that Actavis's Rule 12(b)(6) Motion to Dismiss Demahy's LPLA failure-to-warn

claims under a theory of federal conflict preemption is hereby **DENIED**.

However, to the extent that Demahy's claim constitutes a fraud-on-the-FDA claim against Actavis, that claim is preempted under the Supreme Court's ruling in Buckman Co. v. Plaintiff's Legal Committee, 531 U.S. 341, 348 (2001). Accordingly,

IT IS FURTHER ORDERED that Actavis's Rule 12(b)(6) Motion to Dismiss Demahy's claims, to the extant that they allege fraud-on-the-FDA claims under Louisiana law, is hereby **GRANTED**.

New Orleans, Louisiana this 27th day of October, 2008.

Carl J. Barbier
CARL J. BARBIER
UNITED STATES DISTRICT JUDGE

APPENDIX C

22nd JUDICIAL DISTRICT FOR THE PARISH OF ST. TAMMANY

STATE OF LOUISIANA

No. 2008-12332 Division A

JULIE DEMAHY

VERSUS

WYETH, INC. d/b/a WYETH, individually and as Successor-in-Interest of A. H. ROBINS COMPANY, INC., SCHWARZ PHARMA, INC., and ACTAVIS, INC., Individually and as Successor-in-Interest of PUREPAC PHARMACEUTICAL CO.

FILED: April 28, 2008 S/Evelyn J. Welsh
DEPUTY CLERK

PETITION FOR DAMAGES

NOW INTO COURT, through undersigned counsel, comes petitioner, JULIE DEMAHY, a person of the full age of majority and a resident of and domiciled in St. Tammany Parish, Louisiana, who respectfully submits the following petition for damages:

1

Made defendants herein are:

A. **WYETH, INC. d/b/a WYETH ["WYETH"], Individually and as Successor-in-**

Interest of A.H. ROBINS COMPANY, INC. **WYETH** is a Delaware corporation with its principal place of business at 5 Giraida Farms, Madison, New Jersey 07940, and is the successor-in-interest to A. H. Robins Company, Inc., a Virginia corporation that first obtained approval by the Food and Drug Administration to distribute metoclopramide, under the brand name of Reglan, in the United States. Upon information and belief, until December 27, 2001, **WYETH** manufactured and distributed Reglan through its Wyeth-Ayerst Laboratories Division in St. Davids Pennsylvania. Metoclopramide is the active ingredient of Reglan. Upon information and belief, on December 27, 2001, **WYETH** sold the rights and liabilities associated with Reglan tablets to Schwarz Pharma, Inc. At all material times, **WYETH** was engaged in the business of testing, developing, manufacturing, labeling, marketing, distributing, promoting and/or selling, either directly or indirectly, through third parties, as successor in interest, or related entities, metoclopramide tablets in the State of Louisiana and in interstate commerce.

The registered agent for service for **WYETH** is The Prentice Hall Corp. System, 40 Technology Parkway South, #300, Norcross, Kentucky 30092.

B. **SCHWARZ PHARMA, INC.** **["SCHWARZ"]**, a Delaware corporation. Upon information and belief, on December 27, 2001, **SCHWARZ** purchased the rights and liabilities associated with metoclopramide tablets from **WYETH** pursuant to an Asset Purchase Agreement wherein **SCHWARZ** obligated itself to the responsibility of claims relating to or arising out of

the ingestion or use of metoclopramide from and after March 31, 2002, subject to a right of indemnification by **WYETH**. At all material times, **SCHWARZ** was engaged in the business of testing, developing, manufacturing, labeling, marketing, distributing, promoting and/or selling, either directly or indirectly, through third parties, as successor in interest or related entities, metoclopramide tablets, known by brand name as Reglan, in the State of Louisiana and in interstate commerce.

The registered agent for service for **SCHWARZ** is CSC Entity Services, LLC, 2711 Centerville Road, Suite 400, Wilmington, DE 19808.

C. **ACTAVIS, INC, Individually and as Successor-in-Interest of PUREPAC PHARMACEUTICAL CO. ["ACTAVIS"]**, a Delaware corporation which merged with Purepac Pharmaceutical Co. and as such obligated itself to the responsibility of claims relating to or arising out of the ingestion or use of metoclopramide. At all material times, **ACTAVIS** was engaged in the business of testing, developing, manufacturing, labeling, marketing, distributing, promoting and/or selling, either directly or indirectly, through third parties, as successor in interest, or related entities, metoclopramide tablets, known by brand name as Reglan, in the State of Louisiana and in interstate commerce.

The registered agent for service for **ACTAVIS** is United Corporate Services, INC., 874 Walker Road, Suite C, Dover, DE 19904.

All defendants identified *supra*, inclusive, and each of them, may be referred to in this complaint collectively as the "Defendants" and are liable to plaintiff, individually, jointly, severally, and in solido.

2.

At all relevant times, the Defendants were acting by and through their agents, servants and/or employees, each of whom were acting within the scope and course of their employment by agency or authority on their behalf.

3.

At all relevant times, the Defendants were in the business of researching, designing, formulating, compounding, testing, manufacturing, producing, processing, assembling, inspecting, distributing, marketing, labeling, promoting, packaging and/or advertising the pharmaceutical drugs known and/or branded Reglan and/or the generic equivalent, metoclopramide HCl and/or metoclopramide in the State of Louisiana and in interstate commerce.

4.

At all relevant times, defendants did manufacture, create, design, assemble, test, label, sterilize, package, distribute, promote, supply, market, sell, advertise, and/or otherwise distribute in the State of Louisiana and in interstate commerce Reglan and/or metoclopramide tablets.

5.

At all relevant times, defendants sold, delivered and/or distributed such products for ultimate sale and/or use by consumers, including plaintiff, within the State of Louisiana and in interstate commerce.

6.

This Honorable Court has jurisdiction over this case because the defendants conducted business in the State of Louisiana through pharmaceutical sales representatives and were engaged in testing, developing, manufacturing, labeling, marketing, distributing, promoting and/or selling, either directly or indirectly, through third parties or related entities Reglan and/or metoclopramide tablets; thus, there exists a sufficient nexus between the defendants forum contacts and the plaintiff's claims to justify assertion of jurisdiction in the State of Louisiana.

7.

Venue of this action is proper in this Court as the Parish of St. Tammany, State of Louisiana.

8.

In October 2002, plaintiff's physician prescribed Reglan for the treatment of gastroesophageal reflux disease (GERD).

9.

Plaintiff's pharmacy, Walgreens, filled plaintiff's prescriptions for Reglan with the generic equivalent metoclopramide.

10.

Plaintiff ingested the prescription drug Reglan and/or metoclopramide as prescribed until the end of April 2007.

11.

The terms Reglan and metoclopramide are commonly employed to refer to all metoclopramide products, including the brand name product and its generic equivalents.

12.

Metoclopramides is a prokinetic drug that helps control GERD by blocking dopamine receptors in the brain and throughout the body which enhances movement or contractions of the esophagus, stomach and intestines.

13.

On or about October 19, 2007, plaintiff was evaluated at the University of Texas, Southwestern Medical Center in Dallas, Texas, wherein she was diagnosed as having tardive dyskinesias caused by long-term use of Reglan and/or metoclopramide. That is, plaintiff's long term ingestion of Reglan and/or metoclopramide resulted in overexposure to

the drug which caused her to suffer serious, permanent and disabling neurological injuries, including but not limited to, injuries of or associated with the central nervous and extrapyramidal motor systems, specially Tardive Dyskinesia.

14.

Because of the injuries suffered as a result of her use of Reglan and/or metoclopramide, plaintiff has experienced and will continue to experience medical and related expenses, loss of income, loss of ability to perform household services, disfigurement, disability, pain and suffering, psychological injury and other injuries and damages.

15.

Plaintiff's serious and permanent injuries came about as a foreseeable and proximate result of the Defendants dissemination of inaccurate, misleading, materially incomplete, false and otherwise inadequate information concerning the potential effects of exposure to and ingestion of Reglan and/or metoclopramide to the medical community, physicians, plaintiff's physicians, plaintiff and other foreseeable users of the drug.

16.

Reglan and/or metoclopramide is and was not approved by the United States Food and Drug Administration ["FDA"] for long-term use.

17.

Because of the misleading information that the Defendants provided to physicians and the FDA about the true risks associated with the use of Reglan and/or metoclopramide and because of their failure to adequately inform physicians generally, including plaintiff's physician, about the true risks associated with the use of Reglan and/or metoclopramide, at all relevant times while plaintiff was taking Reglan and/or metoclopramide, her physicians never informed her of any side effects associated with Reglan and/or metoclopramide or that it was only approved by the FDA for short term use of up to 12 weeks.

18.

At all materials times, the Defendants were aware of the serious side effects caused by Reglan and/or metoclopramide including, but not limited to, central system disorders, depression with suicidal ideation, akathisia, tardive dyskinesia, tardive dystonia, visual disturbances and interference with drug metabolism.

19.

Pursuant to FDA regulations, the Defendants knew that they must fully, truthfully and accurately disclose to the FDA data and information regarding the drug's chemistry, proposed manufacturing process, proposed model labeling which includes warnings about risks and side effects, test results for the drug, results of animal studies, results of clinical studies and the drug's bioavailability, because the

data and information would be relied upon by the medical community, physicians, plaintiff's physician, plaintiff and other like foreseeable users of Regan and/or metoclopramide once approved.

20.

The defendants failed to fully, truthfully and accurately disclose Reglan and/or metoclopramide data to the FDA and as a result, intentionally and fraudulently misled the medical community, physicians, plaintiff's physician and plaintiff about the risks associated with long term use of metoclopramide.

21.

Under FDA regulations, the Defendants have a duty to ensure its warnings to the medical community are accurate and adequate; a duty to conduct safety surveillance of adverse events for the drug; and to report any data related to the safety and/or accuracy of the warnings and information disseminated regarding the drug.

22.

The defendants knowingly, intentionally and negligently disseminated misleading information to physicians across the country through the *Physician's Desk Reference*, labeling information for Reglan and/or metoclopramide, which misled the medical community, physicians and plaintiff's physician about the increased risk of extrapyramidal side effects, including tardive dyskinesia.

23.

At all material times, the Defendants knew or should have known that most physicians were not aware of or did not fully appreciate the seriousness of the risks associated with use of Reglan and/or metoclopramide and that, consequently, there was a widespread tendency for physicians to prescribe these drugs for inappropriate long-term use.

24.

The Defendants knew or should have known that the package insert and the Physician's Desk Reference monograph for Reglan did not adequately inform physicians about the risks associated with Reglan and/or metoclopramide.

25.

The Defendants had access to and knew that severe side effects would result from the use of Reglan and/or metoclopramide in the manner in which physicians were prescribing Reglan and/or metoclopramide and the fact that physicians did not fully understand the risks associated with Reglan and/or metoclopramide through the Defendants participation, individually and jointly, in or its ability to review data from clinical studies that were not publicly available, through its review of domestic and international medical literature concerning Reglan and/or metoclopramide, and/or through ongoing litigation.

26.

The Defendants failed to adequately warn physicians about the risks associated with Reglan and/or metoclopramide despite the fact that they knew physicians, the medical community, the generic pharmaceutical industry, plaintiff and others similarly situated relied on defendants to disclose what they knew or should have known from a prudent review of the information they possessed or to which they had access.

27.

Upon information and belief, defendant **WYETH** as Successor-in-Interest of A.H. ROBINS COMPANY, INC. expressly warranted to some physicians that Reglan and/or metoclopramide was safe in long-term use, knowing that physicians would share the information with other physicians in their community and that the physicians would come to rely on the express warranties which were false.

28.

The Defendants knew or should have known, through the exercise reasonable care, that the package insert for Reglan and/or metoclopramide contained false and/or misleading statements and omitted information material to the foreseeable and ordinary contemplated uses of the drugs and, specifically grossly understating the prevalence of acute and long term side effects of Reglan and/or metoclopramide.

29.

The Defendants failed to use reasonable care to modify the package insert to adequately warn physicians about the true risks of both short and long term use, even after several injured patients filed lawsuits alleging inadequate warnings and produced competent expert testimony supporting their allegations.

30.

The Defendants had actual knowledge, through their own studies and studies by independent investigators, that physicians frequently prescribed Reglan and/or metoclopramide for long term use (more than 12 weeks) that was not safe for patients.

31.

The Defendants were further armed with knowledge that research by independent investigations revealed that the risk of tardive dyskensia and other extrapyramidal side effects of Reglan and/or metoclopramide in patients who received the drug for long term use was as much as 100 times greater than the 1 in 500 as disclosed in the package insert and/or the *Physician's Desk Reference.*

32.

The defendants ignored the numerous published and medical literature pertaining to

independent studies concerning the frequency of tardive dyskinesia.

33.

The Defendants had a duty and obligation to disclose to plaintiff and her physicians the true facts concerning Reglan and/or metoclopramide in that it was dangerous and defective and the actual likelihood that it was to cause serious consequences to users, including tardive dyskinesia, and the true level of risk involved in prescribing such drugs for the purposes indicated.

34.

At all material times, the Defendants intentionally, willfully and maliciously concealed or suppressed the true facts concerning Reglan an/or metoclopramide in that long term use and exposure could cause central nervous system side effects, depression with suicidal ideation, akathisia, tardive dyskinesia and tardive dystonia.

35.

At all material times, neither plaintiff nor her physicians were aware of the facts set forth herein and had they been, they would not have acted as they did by utilizing Reglan and/or metoclopramide to treat plaintiff's GERD.

36.

As a proximate result of the concealment or suppression of the facts set forth above, plaintiff was

prescribed and ingested Reglan and/or metoclopramide and subsequently became ill sustaining the injuries and damages set forth above.

37.

The Defendants are liable as the manufacturers, distributors and/or sellers of the drugs Reglan and/or metoclopramide in violation of the Louisiana Products Liability Act, *La. R.S. 9:2800.51, et seq.*

38.

Reglan and/or metoclopramide was defective in design and/or formulation in that, when it left the control of Defendants and/or their representatives, the foreseeable risks of serious harm posed by the drug outweighed its alleged benefits. The foreseeable risks of serious harm were so great that plaintiff, having known of such foreseeable risks and alleged benefits, would not have ingested Reglan and/or metoclopramide.

39.

Reglan and/or metoclopramide was placed into the stream of commerce by Defendants acting through authorized agents, servants, employees and/or representatives. Plaintiff was prescribed Reglan and/or metoclopramide by her physicians and used the drug in a manner foreseeable by Defendants.

40.

The Reglan and/or metoclopramide ingested by plaintiff was expected to and did reach plaintiff without substantial change in its condition as tested, manufactured, designed, labeled, packaged, marketed and distributed. As a result of the use of Reglan and/or metoclopramide, plaintiff suffered serious, permanent and disabling neurological injuries, including but not limited to, injuries of or associated with the central nervous and extrapyramidal motor systems, specifically Tardive Dyskinesia.

41.

Reglan and/or metoclopramide was marketed to physicians to be prescribed to their patients and was marketed and advertised directly to the consuming public. Reglan and/or metoclopramide, as manufactured and supplied to healthcare professionals and the general public, was unaccompanied by proper warnings regarding the serious risks of ingesting the drug. Further, Defendants failed to warn of these serious risks after Defendants had knowledge of same. The information provided to consumers did not reflect Defendants' knowledge that Reglan and/or metoclopramide was not safe and effective as indicated in its aggressive marketing campaign nor were consumers such as plaintiff made aware that ingesting the drug could result in serious, permanent and disabling neurological injuries, including but not limited to, injuries of or associated with the central nervous and extrapyramidal motor systems, specifically Tardive

Dyskinesia. Full and proper warnings that accurately and fully reflected the unreasonable risk of central nervous system side effects, depression, akathisia, akinesia, tardive dyskinesia, tardive dystonia, visual disturbances and/or interference with drug metabolism due to the ingestion of Reglan and/or metoclopramide should have been disclosed by Defendants.

42.

Plaintiff was prescribed Reglan and/or metoclopramide by her physician and used the drug in a manner reasonably foreseeable by Defendants. Reglan and/or metoclopramide was expected to and did reach plaintiff without substantial change in its condition as tested, manufactured, designed, labeled, packaged, marketed and distributed. Plaintiff was not aware of and could not have reasonably discovered the unreasonably dangerous nature of Reglan and/or metoclopramide. As the producing cause and the legal and direct result of the failure to warn consumers of the defective condition of Reglan and/or metoclopramide, as manufactured and supplied by Defendants and their representatives, plaintiff ingested Reglan and/or metoclopramide and subsequently became ill, thereby sustaining the injuries and damages set forth herein.

43.

Defendants, through their agents, servants, employees and/or representatives, employed deception, fraud, false pretense, false promise, misrepresentation, unfair practice and the concealment, suppression, and omission of material

facts in connection with the sale or advertisement of Reglan and/or metoclopramide, in violation of the Louisiana *Unfair Trade Practices and Consumer Protection Law, La. R. S. 51:1401, et seq.*

44.

Defendants' offer for sale of a consumer product, namely Reglan and/or metoclopramide, in trade or commerce, constitutes a representation that the product is reasonably safe for its intended purpose and intended use.

45.

Defendants have engaged in deceptive acts or practices, in violation of the Louisiana *Unfair Trade Practices and Consumer Protection Law*, by knowingly, intentionally and/or recklessly omitting, concealing, and/or suppressing its own data from investigations and clinical trials, other analyses, studies, tests, understandings, and conclusions about the true efficacy and safety of Reglan and/or metoclopramide.

46.

Defendants violated the Louisiana *Unfair Trade Practices and Consumer Protection Law* by intentionally omitting, concealing and/or suppressing, or otherwise failing to communicate and notify the medical community, the plaintiff, and other consumers of Reglan and/or metoclopramide, the negative safety information they possessed.

47.

Defendants deceptive acts were intended to induce the plaintiff to buy Reglan and/or metoclopramide.

48.

Because of the concealment, plaintiff was actually deceived and caused to suffer serious and permanent injuries and actual damages as set forth above.

49.

Defendants made material representations that were false and that were either known to be false when made or were asserted without knowledge of their truth. Defendants possessed adverse drug event reports, drug studies, and other documentation about Reglan and/or metoclopramide yet made numerous misrepresentations regarding the frequency of related adverse occurrences in their package insert or *Physicians Desk Reference* label; as to the existence, occurrences and frequency of occurrences as well as the severity and extent of the overall risk of the drugs use; as to the efficacy of the drugs; as to the number of adverse events with use; and the seriousness and severity of adverse events reported with the use of the drugs.

50.

The misrepresentations by Defendants was the proximate cause and cause-in-fact of plaintiff's injuries.

51.

Defendants owed plaintiff legal duties in connection with their development, manufacturing, and distribution of Reglan and/or metoclopramide. Defendants breached those duties which was the proximate cause and cause in fact of plaintiff's injuries. Specifically, defendants failed to meet their duty to use reasonable care in the testing, creating, designing, manufacturing, labeling, packaging, marketing, selling and warning of Reglan and/or metoclopramide. Defendants are liable for the acts and/or omissions amounting to negligence and/or gross negligence.

WHEREFORE, plaintiff prays that defendants be served with a copy of this petition and duly cited to appear and answer same and after due proceedings, there be judgment rendered in favor of plaintiff, **JULIE DEMAHY**, and against **WYETH, INC. d/b/a WYETH, Individually and as Successor-in-Interest of A.H. ROBINS COMPANY, INC., SCHWARZ PHARMA, INC. AND ACTAVIS INC., individually and as Successor-in-Interest of PUREPAC PHARMACEUTICAL CO.** for all damages listed and considered reasonable in the premises, together with all costs of these proceedings, attorney fees and penalties, and legal interest from the date of judicial demand until paid, and all other general and equitable relief.

Respectfully Submitted,

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PLEASE SERVE (3) – All through Louisiana Long-Arm Statute:

WYETH, INC. d/b/a WYETH, Individually and as Successor-in-Interest of
A.H. ROBINS COMPANY, INC.
Via Louisiana Long-Arm Statute
The Prentice Hall Corp. System
Registered Agent for Wyeth, Inc.
40 Technology Parkway South #300
Norcross, Kentucky 30092

SCHWARZ PHARMA, INC.
Via Louisiana Long-Arm Statute
CSC Entity Services, LLC
Registered Agent for Schwarz Pharma, Inc.
2711 Centerville Road, Suite 400

Wilmington, DE 19808

ACTAVIS, INC.
Via Louisiana Long-Arm Statute
United Corporate Services, Inc.
Registered Agent for Actavis, Inc.
874 Walker Road, Suite C
Dover, DE 19904

A TRUE COPY

Evelyn J. Welsh
DY. CLERK 22nd JUD. DIST. COURT
ST. TAMMANY PARISH, LA

APPENDIX D

U.S. Constitution, Art. VI, clause 2

This Constitution, and the Laws of the United States which shall be made in Pursuance thereof; and all Treaties made, or which shall be made, under the Authority of the United States, shall be the supreme Law of the Land; and the Judges in every State shall be bound thereby, any Thing in the Constitution or Laws of any State to the Contrary notwithstanding.

21 U.S.C. § 355

(a) Necessity of effective approval of application

No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) of this section is effective with respect to such drug.

(b) Filing application; contents.

(1) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a). Such person shall submit to the Secretary as a part of the application (A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (B) a full list of the articles used as components of such drug; (C) a full statement of the composition of such drug; (D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (E) such

samples of such drug and of the articles used as components thereof as the Secretary may require; (F) specimens of the labeling proposed to be used for such drug and (G) any assessments required under section 505B. The applicant shall file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture use, or sale of the drug. If an application is filed under this subsection for a drug and a patent which claims such drug or a method of using such drug is issued after the filing date but before approval of the application, the applicant shall amend the application to include the information required by the preceding sentence. Upon approval of the application, the Secretary shall publish information submitted under the two preceding sentences. The Secretary shall, in consultation with the Director of the National Institutes of Health and with representatives of the drug manufacturing industry, review and develop guidance, as appropriate, on the inclusion of women and minorities in clinical trials required by clause (A), and (G) any assessments required under section 355c of this title.

* * *

(j) Abbreviated new drug applications

(1) Any person may file with the Secretary an abbreviated application for the approval of a new drug.

(2) (A) An abbreviated application for a new drug shall contain—

(i) information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a drug listed under paragraph (7) (hereinafter in this subsection referred to as a "listed drug");

(ii) (I) if the listed drug referred to in clause (i) has only one active ingredient, information to show that the active ingredient of the new drug is the same as that of the listed drug;

(II) if the listed drug referred to in clause (i) has more than one active ingredient, information to show that the active ingredients of the new drug are the same as those of the listed drug, or

(III) if the listed drug referred to in clause (i) has more than one active ingredient and if one of the active ingredients of the new drug is different and the application is filed pursuant to the approval of a petition filed under subparagraph (C), information to show that the other active ingredients of the new drug are the same as the active ingredients of the listed drug, information to show that the different active ingredient is an active ingredient of a listed drug or of a drug which does not meet the requirements of section 321 (p) of this title, and such other information respecting the different active

ingredient with respect to which the petition was filed as the Secretary may require;

(iii) information to show that the route of administration, the dosage form, and the strength of the new drug are the same as those of the listed drug referred to in clause (i) or, if the route of administration, the dosage form, or the strength of the new drug is different and the application is filed pursuant to the approval of a petition filed under subparagraph (C), such information respecting the route of administration, dosage form, or strength with respect to which the petition was filed as the Secretary may require;

(iv) information to show that the new drug is bioequivalent to the listed drug referred to in clause (i), except that if the application is filed pursuant to the approval of a petition filed under subparagraph (C), information to show that the active ingredients of the new drug are of the same pharmacological or therapeutic class as those of the listed drug referred to in clause (i) and the new drug can be expected to have the same therapeutic effect as the listed drug when administered to patients for a condition of use referred to in clause (i);

(v) information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug referred to in clause (i) except for changes required because of differences approved under a petition filed under subparagraph (C) or because the new drug and the listed drug are produced or distributed by different manufacturers;

(vi) the items specified in clauses (B) through (F) of subsection (b)(1) of this section;

(vii) a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the listed drug referred to in clause (i) or which claims a use for such listed drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under subsection (b) or (c) of this section—

(I) that such patent information has not been filed,

(II) that such patent has expired,

(III) of the date on which such patent will expire, or

(IV) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted; and

(viii) if with respect to the listed drug referred to in clause (i) information was filed under subsection (b) or (c) of this section for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use.

The Secretary may not require that an abbreviated application contain information in addition to that required by clauses (i) through (viii).

* * *

(4) Subject to paragraph (5), the Secretary shall approve an application for a drug unless the Secretary finds—

(A) the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity;

(B) information submitted with the application is insufficient to show that each of the proposed conditions of use have been previously approved for the listed drug referred to in the application;

(C) (i) if the listed drug has only one active ingredient, information submitted with the application is insufficient to show that the active ingredient is the same as that of the listed drug;

(ii) if the listed drug has more than one active ingredient, information submitted with the application is insufficient to show that the active ingredients are the same as the active ingredients of the listed drug, or

(iii) if the listed drug has more than one active ingredient and if the application is for a drug which has an active ingredient different from the listed drug, information submitted with the application is insufficient to show—

(I) that the other active ingredients are the same as the active ingredients of the listed drug, or

(II) that the different active ingredient is an active ingredient of a listed drug or a drug which does not meet the requirements of section 321 (p) of this title,

or no petition to file an application for the drug with the different ingredient was approved under paragraph (2)(C);

(D) (i) if the application is for a drug whose route of administration, dosage form, or strength of the drug is the same as the route of administration, dosage form, or strength of the listed drug referred to in the application, information submitted in the application is insufficient to show that the route of administration, dosage form, or strength is the same as that of the listed drug, or

(ii) if the application is for a drug whose route of administration, dosage form, or strength of the drug is different from that of the listed drug referred to in the application, no petition to file an application for the drug with the different route of administration, dosage form, or strength was approved under paragraph (2)(C);

(E) if the application was filed pursuant to the approval of a petition under paragraph (2)(C), the application did not contain the information required by the Secretary respecting the active ingredient, route of administration, dosage form, or strength which is not the same;

(F) information submitted in the application is insufficient to show that the drug is bioequivalent to the listed drug referred to in the application or, if the

application was filed pursuant to a petition approved under paragraph (2)(C), information submitted in the application is insufficient to show that the active ingredients of the new drug are of the same pharmacological or therapeutic class as those of the listed drug referred to in paragraph (2)(A)(i) and that the new drug can be expected to have the same therapeutic effect as the listed drug when administered to patients for a condition of use referred to in such paragraph;

(G) information submitted in the application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug referred to in the application except for changes required because of differences approved under a petition filed under paragraph (2)(C) or because the drug and the listed drug are produced or distributed by different manufacturers;

(H) information submitted in the application or any other information available to the Secretary shows that (i) the inactive ingredients of the drug are unsafe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug, or (ii) the composition of the drug is unsafe under such conditions because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included;

(I) the approval under subsection (c) of this section of the listed drug referred to in the application under this subsection has been withdrawn or suspended for grounds described in the first sentence of subsection

(e) of this section, the Secretary has published a notice of opportunity for hearing to withdraw approval of the listed drug under subsection (e) of this section for grounds described in the first sentence of subsection (e) of this section, the approval under this subsection of the listed drug referred to in the application under this subsection has been withdrawn or suspended under paragraph (6), or the Secretary has determined that the listed drug has been withdrawn from sale for safety or effectiveness reasons;

(J) the application does not meet any other requirement of paragraph (2)(A); or

(K) the application contains an untrue statement of material fact.

* * *

(k) Records and reports; required information; regulations and orders; access to records

(1) In the case of any drug for which an approval of an application filed under subsection (b) or (j) of this section is in effect, the applicant shall establish and maintain such records, and make such reports to the Secretary, of data relating to clinical experience and other data or information, received or otherwise obtained by such applicant with respect to such drug, as the Secretary may by general regulation, or by order with respect to such application, prescribe on the basis of a finding that such records and reports are necessary in order to enable the Secretary to determine, or facilitate a determination, whether

there is or may be ground for invoking subsection (e) of this section. Regulations and orders issued under this subsection and under subsection (i) of this section shall have due regard for the professional ethics of the medical profession and the interests of patients and shall provide, where the Secretary deems it to be appropriate, for the examination, upon request, by the persons to whom such regulations or orders are applicable, of similar information received or otherwise obtained by the Secretary.

* * *

21 C.F.R. § 314.3

Sec. 314.3 Definitions.

(a) The definitions and interpretations contained in section 201 of the act apply to those terms when used in this part.

(b) The following definitions of terms apply to this part:

Abbreviated application means the application described under 314.94, including all amendments and supplements to the application. "Abbreviated application" applies to both an abbreviated new drug application and an abbreviated antibiotic application.

* * *

21 C.F.R. § 314.70

Supplements and other changes to an approved application.

(a) *Changes to an approved application.*

(1)(i) Except as provided in paragraph (a)(1)(ii) of this section, the applicant must notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application. The notice is required to describe the change fully. Depending on the type of change, the applicant must notify FDA about the change in a supplement under paragraph (b) or (c) of this section or by inclusion of the information in the annual report to the application under paragraph (d) of this section.

(ii) The submission and grant of a written request for an exception or alternative under 201.26 of this chapter satisfies the applicable requirements in paragraphs (a) through (c) of this section. However, any grant of a request for an exception or alternative under 201.26 of this chapter must be reported as part of the annual report to the application under paragraph (d) of this section.

(2) The holder of an approved application under section 505 of the act must assess the effects of the change before distributing a drug product made with a manufacturing change.

(3) Notwithstanding the requirements of paragraphs (b) and (c) of this section, an applicant must make a change provided for in those paragraphs in accordance with a regulation or guidance that provides for a less burdensome notification of the change (for example, by submission of a supplement

that does not require approval prior to distribution of the product or in an annual report).

(4) The applicant must promptly revise all promotional labeling and advertising to make it consistent with any labeling change implemented in accordance with paragraphs (b) and (c) of this section.

(5) Except for a supplement providing for a change in the labeling, the applicant must include in each supplement and amendment to a supplement providing for a change under paragraph (b) or (c) of this section a statement certifying that a field copy has been provided in accordance with 314.440(a)(4).

(6) A supplement or annual report must include a list of all changes contained in the supplement or annual report. For supplements, this list must be provided in the cover letter.

***

(c) *Changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change (moderate changes).* (1) A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. If the supplement provides for a labeling change under paragraph (c)(6)(iii) of this section, 12 copies of the final printed labeling must be included.

(2) These changes include, but are not limited to:

(i) A change in the container closure system that does not affect the quality of the drug product, except those described in paragraphs (b) and (d) of this section; and

(ii) Changes solely affecting a natural protein, a recombinant DNA-derived protein/polypeptide or a complex or conjugate of a drug substance with a monoclonal antibody, including:

(A) An increase or decrease in production scale during finishing steps that involves different equipment; and

(B) Replacement of equipment with that of a different design that does not affect the process methodology or process operating parameters.

(iii) Relaxation of an acceptance criterion or deletion of a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements.

(3) A supplement submitted under paragraph (c)(1) of this section is required to give a full explanation of the basis for the change and identify the date on which the change is to be made. The supplement must be labeled "Supplement--Changes Being Effected in 30 Days" or, if applicable under paragraph (c)(6) of this section, "Supplement--Changes Being Effected."

(4) Pending approval of the supplement by FDA, except as provided in paragraph (c)(6) of this section, distribution of the drug product made using the change may begin not less than 30 days after receipt of the supplement by FDA. The information listed in paragraphs (b)(3)(i) through (b)(3)(vii) of this section must be contained in the supplement.

(5) The applicant must not distribute the drug product made using the change if within 30 days following FDA's receipt of the supplement, FDA informs the applicant that either:

(i) The change requires approval prior to distribution of the drug product in accordance with paragraph (b) of this section; or

(ii) Any of the information required under paragraph (c)(4) of this section is missing; the applicant must not distribute the drug product made using the change until the supplement has been amended to provide the missing information.

(6) The agency may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved application may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change. These changes include, but are not limited to:

(i) Addition to a specification or changes in the methods or controls to provide increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity,

or potency that it purports or is represented to possess;

(ii) A change in the size and/or shape of a container for a nonsterile drug product, except for solid dosage forms, without a change in the labeled amount of drug product or from one container closure system to another;

(iii) Changes in the labeling to reflect newly acquired information, except for changes to the information required in 201.57(a) of this chapter (which must be made under paragraph (b)(2)(v)(C) of this section), to accomplish any of the following:

(A) To add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling under 201.57(c) of this chapter;

(B) To add or strengthen a statement about drug abuse, dependence, psychological effect, or overdosage;

(C) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product;

(D) To delete false, misleading, or unsupported indications for use or claims for effectiveness; or

(E) Any labeling change normally requiring a supplement submission and approval prior to

distribution of the drug product that FDA specifically requests be submitted under this provision.

(7) If the agency disapproves the supplemental application, it may order the manufacturer to cease distribution of the drug product(s) made with the manufacturing change.

21 C.F.R. § 314.94

Content and format of an abbreviated application.

Abbreviated applications are required to be submitted in the form and contain the information required under this section. Three copies of the application are required, an archival copy, a review copy, and a field copy. FDA will maintain guidance documents on the format and content of applications to assist applicants in their preparation.

(a) *Abbreviated new drug applications.* Except as provided in paragraph (b) of this section, the applicant shall submit a complete archival copy of the abbreviated new drug application that includes the following:

* * *

(8) *Labeling*-- (i) *Listed drug labeling.* A copy of the currently approved labeling (including, if applicable, any Medication Guide required under part 208 of this chapter) for the listed drug referred to in the abbreviated new drug application, if the abbreviated new drug application relies on a reference listed drug.

(ii) *Copies of proposed labeling.* Copies of the label and all labeling for the drug product including, if applicable, any Medication Guide required under part 208 of this chapter (4 copies of draft labeling or 12 copies of final printed labeling).

(iii) *Statement on proposed labeling.* A statement that the applicant's proposed labeling including, if applicable, any Medication Guide required under part 208 of this chapter is the same as the labeling of the reference listed drug except for differences annotated and explained under paragraph (a)(8)(iv) of this section.

(iv) *Comparison of approved and proposed labeling.* A side-by-side comparison of the applicant's proposed labeling including, if applicable, any Medication Guide required under part 208 of this chapter with the approved labeling for the reference listed drug with all differences annotated and explained. Labeling (including the container label, package insert, and, if applicable, Medication Guide) proposed for the drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers. Such differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect

of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act.

21 C.F.R. § 314.97

Supplements and other changes to an approved abbreviated application.

The applicant shall comply with the requirements of §§ 314.70 and 314.71 regarding the submission of supplemental applications and other changes to an approved abbreviated application.

* * *

21 C.F.R. § 314.150

Withdrawal of approval of an application or abbreviated application.

* * *

b) FDA may notify the applicant, and, if appropriate, all other persons who manufacture or distribute identical, related, or similar drug products as defined in § 310.6, and for a new drug afford an opportunity for a hearing on a proposal to withdraw approval of the application or abbreviated new drug application under section 505(e) of the act and under the procedure in § 314.200, if the agency finds:

* * *

(10) That the labeling for the drug product that is the subject of the abbreviated new drug application is no longer consistent with that for the listed drug referred to in the abbreviated new drug application, except for differences approved in the abbreviated new drug application or those differences resulting from: (i) A patent on the listed drug issued after approval of the abbreviated new drug application; or (ii) Exclusivity accorded to the listed drug after approval of the abbreviated new drug application that do not render the drug product less safe or effective than the listed drug for any remaining, nonprotected condition(s) of use.

OPPOSITION BRIEF

SUPREME COURT, U.S.
FILED
JUL 30 2010
OFFICE OF THE CLERK

No. 09-1501

IN THE

Supreme Court of the United States

ACTAVIS, INC.,

Petitioner,

v.

JULIE DEMAHY,

Respondent.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Fifth Circuit

RESPONDENT'S BRIEF IN OPPOSITION

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QUESTION PRESENTED

Are the states preempted under the Supremacy Clause of the Constitution from requiring additional safety information on a generic product label where the brand has not changed its label?

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RESPONDENT'S BRIEF IN OPPOSITION

Respondent Julie Demahy respectfully requests that this Court deny the petition for review of the decision of the United States Court of Appeals for the Fifth Circuit, which held that Ms. Demahy's state products liability claims against the manufacturer of the generic drug that injured her are not impliedly preempted by the Food, Drug and Cosmetic Act (FDCA), or the Hatch-Waxman Amendments thereto.

The petition for certiorari improperly seeks an advisory opinion from this Court. The court of appeals identified three bases for denying preemption, yet Petitioner has sought review of only one. Thus, even if this Court were to agree with Petitioner, the outcome of the case would not change.

Moreover, the decision below does not conflict with any decision of any federal court of appeals or state court of last resort, and it is consistent with relevant decisions of this Court. In fact, the decision below is a straightforward application of the reasoning in this Court's decision last term in *Wyeth v. Levine*, ... U.S. ----, 129 S. Ct. 1187 (2009), to a state failure-to-warn suit brought against manufacturers of a generic drug. Every court to take up the question since the *Levine* decision has concluded that state failure-to-warn claims against generic drug companies are not preempted.

Petitioner seeks a special immunity from liability for generic drug companies, an immunity that is not available to name-brand drug companies or other manufacturers. Given that more than seventy percent of all prescriptions are now filled

with generic drugs, preemption of state tort claims against such companies would leave most persons injured by inadequately labeled drugs, including Ms. Demahy, remediless. Congress's silence regarding preemption of these cases is "powerful evidence that Congress did not intend" such a draconian result. *Id.* at 1200.

COUNTERSTATEMENT OF THE CASE

Julie Demahy developed tardive dyskinesia, a severe and irreversible neurological disorder, as a result of her long-term use of the prescription drug metoclopramide, which was prescribed to treat her gastroesophageal reflux. At the time,[1] the metoclopramide label indicated that the risk of any "extrapyramidal symptom" from metoclopramide use, including tardive dyskinesia, was "approximately 1 in 500 patients." In fact, the actual incidence of tardive dyskinesia in patients using metoclopramide long-term was many times higher, perhaps as high as 1 in 5 patients.

Despite mounting evidence that the risks of tardive dyskinesia were much greater than reflected in the product label, no manufacturer of metoclopramide ever proposed to the Food and Drug Administration (FDA) that the warnings on the metoclopramide label should be changed to reflect that greater risk. In February 2009, too late for Ms. Demahy, the FDA—acting on its own initiative pursuant to powers granted to the agency in the Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (2007) (FDAAA)—ordered manufacturers of metoclopramide

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[1] Ms. Demahy took metoclopramide from October 2002 through April 2007. Pet. App. 96a-97a.

to add a "Boxed Warning" to their labels. That warning states, in relevant part: "Prolonged treatment (greater than 12 weeks) with metoclopramide should be avoided in all but rare cases where therapeutic benefit is thought to outweigh the risks to the patient of developing tardive dyskinesia."

Ms. Demahy sued Petitioner Actavis, Inc. (Actavis), the manufacturer of the generic metoclopramide she had used, for failure to adequately warn her of the risks of long-term metoclopramide use.[2] Actavis moved to dismiss Ms. Demahy's claims on the ground of implied conflict preemption. The district court, ruling before *Wyeth v. Levine* was decided, denied Actavis's motion, but certified the issue for interlocutory appeal pursuant to 28 U.S.C. § 1292(b) (2010).

The Fifth Circuit, following *Levine*, unanimously affirmed, ruling that Congress had not intended to preempt such state tort claims against generic drug companies. The court of appeals concluded that the plaintiff's failure-to-warn claims were not preempted because the generic-drug-company defendant could have sought to strengthen its warnings through either the "Changes Being Effected" (CBE) process or the prior approval process or by sending warnings directly to health care providers. Pet. App. 23a-35a. The court rejected the argument that the responsibility for strengthening label warnings rested solely on the name-brand drug company:

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[2] She also sued the manufacturers of the name-brand version of metoclopramide, Reglan, but voluntarily dismissed those defendants after establishing that Ms. Demahy had not taken the name-brand drug. Pet. App. 3a n.4.

> The federal interest is in maintaining safe and effective labeling that is consistent across name brand and generic bioequivalent versions of the same drug. *Who* prompts the FDA to consider necessary changes to that shared label is immaterial.

Id. at 36a (emphasis in original).

Federal Regulation of Generic Drugs

As this Court recognized in *Levine*, "it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. It is charged both with crafting an adequate label and with ensuring that its warnings remain adequate." 129 S. Ct. at 1197-98.

This principle applies with equal force to both name-brand and generic drug companies. All drug companies are under a statutory obligation to maintain adequate warnings on their labels. 21 U.S.C. § 352(f)(2) (2010) (Opp'n App. 1a) ("A drug . . . shall be deemed to be misbranded . . . unless its labeling bears . . . such adequate warnings against use . . . where its use may be dangerous . . . as are necessary for the protection of users"). Both name-brand and generic drug manufacturers have an obligation to revise their labels "to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved." 21 C.F.R. § 201.57(e) (2005) (Opp'n App. 2a).[3] As the FDA has

[3] In 2006, the FDA issued amended labeling regulations for prescription drugs. 71 Fed. Reg. 3,922 (Jan. 24, 2006). That

specifically instructed manufacturers of generic drugs, "[a]fter approval of an [Abbreviated New Drug Application], if an ANDA holder believes that new safety information should be added, it should provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised". 57 Fed. Reg. 17,950, 17,961 cmt. 40 (Apr. 28, 1992).[4]

As this Court recognized in *Levine*, a new warning may be justified by adverse drug experience reports, 129 S. Ct. at 1197, which all drug manufacturers are required to collect and report to the FDA. 21 C.F.R. §§ 314.80 (NDA holders) & 314.98 (2010) (ANDA holders). Reports in the medical literature can also provide evidence to support a labeling change; indeed, the FDA letters

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rulemaking, which became effective on June 30, 2006, redesignated § 201.57(e) as 21 C.F.R. § 201.80(e) (2010) and it remains the regulatory standard for drugs labeled under the old labeling rules, such as metoclopramide. 71 Fed. Reg. at 3,988, 3,996. A virtually identical requirement applies to drugs labeled under the new regulation. 21 C.F.R. § 201.57(c)(6)(i) (2010) ("In accordance with §§ 314.70 and 601.12 of this chapter, the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitively established."). 71 Fed. Reg. at 3,990.

[4] Every time a generic drug company submits an ANDA application, amendment, or supplement, it must certify to the FDA that it will, *inter alia*, "update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling." Department of Health and Human Services, Food and Drug Administration, *Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use*, Form FDA 356h (Oct. 2005), *available at* http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM082348.pdf.

ordering manufacturers of metoclopramide to add a boxed warning justified the change by referencing published studies. *See* Letter from Joyce Korvick, Center for Drug Evaluation and Research (CDER), FDA, to NDA holders for Reglan 1 & nn.1-3 (Feb. 26, 2009) *available at* http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM111376.pdf; Letter from Gary Buehler, CDER, FDA, to ANDA holders for metoclopramide 1-2 & nn.1-3 (Feb. 26, 2009), *available at* http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM111378.pdf. A manufacturer's own clinical trials can also provide evidence to support labeling changes, but such studies "are in no way prerequisites to those changes." Pet. App. 41a.

There are two formal procedures by which both brand-name and generic drug companies may seek to revise their labels: (1) a Prior Approval Supplement, required for "Major Changes," 21 C.F.R. § 314.70(b) (2005) (Opp'n App. 3a), or (2) a Changes Being Effected (CBE) Supplement for "Moderate Changes," 21 C.F.R. § 314.70(c) (2005) (Opp'n App. 5a), under which a manufacturer may proceed with the change upon notification to the agency, but which the FDA may later disapprove. Labeling changes to "add or strengthen a contra-indication, warning, precaution, or adverse reaction," may be made through the CBE process. 21 C.F.R. § 314.70(c)(6)(iii)(A) (2005).[5] Notably, 21 C.F.R. § 314.97 (2010) instructs generic drug companies to follow the procedures of § 314.70 "regarding the

[5] The petition appendix includes portions of the current version of § 314.70, rather than the version in effect during the time at issue in this litigation.

submission of supplemental applications and other changes to an approved abbreviated application."

In addition to revising a product label, a drug company may provide new warnings to health care professionals by other means, such as a "Dear Doctor" letter. 44 Fed. Reg. 37,434, 37,447 (June 26, 1979).

Thus, drug labels are not fixed as of the date of FDA approval. Nor should they be: Name-brand drugs receive initial approval based upon very limited clinical trials and there is a substantial likelihood that new risks, complications, and contraindications will only be identified or confirmed after the drug—and its generic equivalents—have been prescribed more widely. *See* Karen E. Lasser, *et al.*, *Timing of New Black Box Warnings and Withdrawals for Prescription Medications*, 287 J.A.M.A. 2215, 2218 (May 1, 2002) ("Only half of newly discovered serious ADRs are detected and documented in the Physicians' Desk Reference within 7 years after drug approval."). For this reason, FDA regulations reasonably require each drug company to provide physicians and patients with up-to-date warnings and precautions as long as the product is being marketed and prescribed to patients. 21 U.S.C. § 352(f)(2); 21 C.F.R. §§ 201.57(c)(6)(i), 201.80(e).

REASONS FOR DENYING THE PETITION

I. THE PETITION IMPROPERLY SEEKS AN ADVISORY OPINION FROM THIS COURT

This Court has repeatedly instructed litigants that it has no warrant to issue advisory opinions.

See, e.g., *Herb v. Pitcairn*, 324 U.S. 117, 126 (1945) ("We are not permitted to render an advisory opinion, and if the same judgment would be rendered by the state court after we corrected its views of federal laws, our review could amount to nothing more than an advisory opinion."). Here, even if this Court were to resolve the Question Presented favorably to Petitioner, the lower court's determination that Petitioner had other available means, consistent with FDA regulations, to advise health-care providers of dangers from its drug would remain unchanged and thus Ms. Demahy's claims still would not be preempted. Because the same judgment would stand, what Petitioner seeks would "amount to nothing more than an advisory opinion."

The court of appeals concluded that there were at least three separate routes Petitioner could have taken to warn health care providers of the heightened risk of tardive dyskinesia from prolonged metoclopramide use: the "Changes Being Effected" process, the Prior Approval process, or warnings sent directly to health care providers. Pet. App. 23a-35a. As the court recognized: "A finding of preemption would require that all be foreclosed to generic manufacturers." Pet. App. 23a.

Petitioner, however, has expressly limited its petition to a challenge to the court of appeals' determination that a generic drug company can invoke the CBE process. Pet. 8 n.4 (The issue whether a generic drug company "could have proposed a labeling change to the FDA . . . is raised in the *Mensing* petitions, but Petitioner has limited this petition to the issue of preemption of a state requirement that the generic change its label where the brand has not."). As the Fifth Circuit opinion

notes: "Even assuming that the CBE regulation cannot be used by an ANDA holder to amend its label without FDA pre-approval, *Levine*'s principles still apply with full force, and we agree with Demahy that generic drug manufacturers may use two other means of complying with both federal and state law . . . ." Pet. App. 36a-37a.

Because the answer to the question presented would not affect the outcome of the case, the petition seeks nothing more than an advisory opinion and should be denied.

II. THERE IS NO CONFLICT AMONG THE UNITED STATES COURTS OF APPEALS AND/OR STATE COURTS OF LAST RESORT

Review is also unwarranted because there is no conflict among the lower courts with regard to whether federal law preempts failure-to-warn claims involving generic drugs. To date, three federal courts of appeals—the Fourth, Fifth, and Eighth Circuits—have addressed the issue of generic drug companies' potential liability for failure to warn of the risks posed by their products; each has concluded, without dissent, that the federal regulatory scheme permits generic drug companies to strengthen label warnings and that such companies may be held liable under state law for inadequate warnings.[6]

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[6] As Petitioner notes, the issue of preemption of state claims against generic drug manufacturers is pending before both the Sixth and Ninth Circuits. *Morris v. Wyeth, Inc.*, No. 09-5460 (6th Cir. filed Apr. 27, 2009); *Smith v. Wyeth, Inc.*, No. 09-5460 (6th Cir. filed Apr. 16, 2009); *Wilson v. Pliva, Inc.*, No. 09-5466 (6th Cir. filed Apr. 20, 2009); *Gaeta v. Perrigo Pharm. Co.*, No. 09-15001 (9th Cir. filed Jan. 6, 2009). To Respondent's

Shortly before the decision below, the Eighth Circuit became the first court of appeals to apply *Levine* to state tort claims against generic drug companies and deny their preemption defense. *Mensing v. Wyeth, Inc.*, 588 F.3d 603 (8th Cir. 2009), *petitions for cert. filed* 78 U.S.L.W. 3522 (Feb. 19, 2010) (No. 09-993), 78 U.S.L.W. 3523 (Feb. 25, 2010) (No. 09-1039). The Eighth Circuit rejected the argument that generic drug companies are powerless to initiate stronger warnings about the drugs they sell: "Far from prohibiting them from taking steps to warn their customers of new safety hazards, federal law requires such action." *Id.* at 614. The *Mensing* court added, "Congress could have crafted a preemption provision for generic drugs in its 1984 amendments, having done so for medical devices less than 10 years earlier. It chose not to do that." *Id.* at 607.

Even before *Levine*, the Fourth Circuit reached a similar conclusion regarding a generic drug company's potential liability for inadequate warnings. In *Foster v. American Home Products Corp.*, 29 F.3d 165 (4th Cir. 1994), that court opined:

> When a generic manufacturer adopts a name brand manufacturer's warnings and representations without independent investigation, it does so at the risk that such warnings and representations may be flawed. . . . The statutory scheme governing premarketing approval for drugs simply does not evidence Congressional intent

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knowledge, no case raising the issue has reached the highest court of any state.

> to insulate generic drug manufacturers from liability for misrepresentations made regarding their products, or to otherwise alter state products liability law. Manufacturers of generic drugs, like all other manufacturers, are responsible for the representations they make regarding their products.

Id. at 169-70.

Every court of appeals to address this question has reached the same conclusion. The absence of conflict in the lower courts strongly supports denial of the petition for certiorari.

III. THE LOWER COURTS ARE NOT CONFUSED ABOUT THE APPLICATION OF *WYETH V. LEVINE* TO CLAIMS AGAINST GENERIC DRUG COMPANIES

As the foregoing discussion demonstrates, the Fifth and Eighth Circuits have had no problem applying the lessons of *Levine* to preemption defenses asserted by generic drug companies: both courts recognized that that decision carried "important implications" for generic drug companies as well. Pet. App. 10a. They are not alone in finding the application of preemption doctrine clear in this context. More than a dozen courts have taken up the issue of preemption of state-law tort claims against generic drug manufacturers since *Wyeth v. Levine* was decided. Every one of them has concluded that the plaintiffs' claims are not preempted. *See, e.g.*, *Demahy*, Pet. App. 1a; *Mensing v. Wyeth*, 588 F.3d 603; *Dorsett v. Sandoz, Inc.*, No. CV06-7821, 2010 WL 1174204 (C.D. Cal. Mar. 26, 2010); *Succegood v.*

Pliva, Inc., No. 1:07-cv-1671, 2010 WL 1138455 (N.D. Ga. Mar. 22, 2010); *Weilbrenner v. Teva Pharm. USA, Inc.*, No. 7:08-CV-23, 2010 WL 924915 (M.D. Ga. Mar. 10, 2010); *Vitatoe v. Mylan Pharm., Inc.*, No. 1:08cv85, 2010 WL 1008788 (N.D. W. Va. Mar. 5, 2010); *Fulgenzi v. Wyeth, Inc.*, No. 5:09CV1767, 2010 WL 649349 (N.D. Ohio Feb. 19, 2010); *Munroe v. Barr Labs.*, 670 F. Supp. 2d 1299, 1303 (N.D. Fla. 2009); *Bartlett v. Mutual Pharm. Co.*, 659 F. Supp. 2d 279 (D.N.H. 2009); *Stacel v. Teva Pharm., USA*, 620 F. Supp. 2d 899, 907 (N.D. Ill. 2009); *Schrock v. Wyeth*, 601 F. Supp. 2d 1262, 1265 (W.D. Okla. 2009); *Couick v. Wyeth, Inc.*, No. 3:09-CV-210-RJC-DSC, 2009 WL 4644394 (W.D.N.C. Dec. 7, 2009); *Pustejovsky v. Wyeth*, No. 4:07-CV-103-Y, 2009 WL 3336032, at *1 n.4 (N.D. Tex. Sept. 4, 2009); *see also In re Budeprion XL Marketing & Sales Litig.*, No. 09-md-2107, 2010 WL 2135625 (E.D. Pa. May 26, 2010) (rejecting preemption defense in consumer fraud class action against generic drug companies); *Kellogg v. Wyeth*, 612 F. Supp. 2d 437, 442 (D. Vt. 2009) (post-*Levine* decision declining to certify for interlocutory appeal a pre-*Levine* ruling denying preemption).

In short, the lower courts have had no difficulty applying *Levine's* teachings. Accordingly, this Court's review is not needed to provide guidance on the question presented.

IV. PETITIONER SEEKS SPECIAL PROTECTION FROM TORT LIABILITY THAT IS NOT AVAILABLE TO OTHER MANUFACTURERS AND THAT FINDS NO SUPPORT IN THE HATCH-WAXMAN AMENDMENTS

It should not be surprising, especially in the wake of *Levine*, that the lower courts have had little difficulty rejecting preemption claims by generic drug companies. Petitioner seeks a special shield against tort liability that is not available to other manufacturers, including the manufacturers of name-brand drugs. Over seventy percent of prescriptions in this country are today filled with generic drugs. Susan Okie, *Multinational Medicines—Ensuring Drug Quality in an Era of Global Manufacturing*, 361 New Eng. J. Med. 737, 738 (2009). A finding of preemption would leave all consumers of inadequately labeled generic drugs, including Ms. Demahy, without legal remedy. As the court below observed, it would be a "bizarre conclusion that Congress intended to implicitly deprive a plaintiff whose doctor prescribes a generic drug of *any* remedy, while under *Levine*, that same plaintiff would have a state-law claim had she only demanded a name brand drug instead." Pet. App. 45a. "If Congress had intended to deprive injured parties of a long available form of compensation, it surely would have expressed that intent more clearly." *Bates v. Dow Agrosciences LLC*, 544 U.S. 431, 449 (2005).

The FDCA is, first and foremost, a safety statute. As both the Fifth and Eighth Circuits recognized, the Hatch-Waxman Amendments, while providing for simplified, expedited approval of

generic drugs, did not depart from "the fundamental requirement of the FDCA that all marketed drugs remain safe." *Mensing*, 588 F.3d at 612; Pet. App. 44a. State-law remedies complement federal regulation "by motivating manufacturers to produce safe and effective drugs and to give adequate warnings." *Levine*, 129 S. Ct. at 1200.

Despite the alarmist tone of the petition, the Fifth Circuit's decision does not threaten to drive generic drugs off the market or to endanger the viability of the generic drug industry. Suits against drug manufacturers for inadequate warnings have existed since long before there was an FDA, *see, e.g.*, *Thomas v. Winchester*, 6 N.Y. 397 (1852), and the generic drug industry has thrived despite the risk of tort liability.

Generic drug companies need not undertake expensive clinical trials to protect themselves from liability. All they need do is review the adverse drug experience reports they already receive, and monitor the medical literature for studies identifying new risks associated with the products they sell. Pet. App. 40a-43a; *Mensing*, 588 F.3d at 611-12. If the name-brand company is properly strengthening its label warnings "as soon as there is reasonable evidence of an association of a serious hazard with a drug," 21 C.F.R. § 201.80(e), a generic competitor can simply tag along with those label changes; but where the name-brand manufacturer fails to propose necessary warnings, the generic drug companies cannot just rely upon that inaction: "In these circumstances, § 201.57(e) [now 21 C.F.R. § 201.80(e)] does not permit generic manufacturers passively to accept the inadequacy of their drug's

label as they market and profit from it." *Mensing*, 588 F.3d at 609.

Neither the Hatch-Waxman Amendments nor its legislative history contains any hint that Congress intended to shield generic drug companies from state-law liability. Congress's decision not to include an express preemption provision in those amendments—only eight years after it had expressly preempted certain state claims against defective medical devices—"militates further against a finding of preemption here." Pet. App. 14a. As this Court said in *Levine*:

> If Congress thought state-law suits posed an obstacle to its objectives, it surely would have enacted an express pre-emption provision at some point during the FDCA's 70-year history. . . . Its silence on this issue, coupled with its certain awareness of the prevalence of state tort litigation, is powerful evidence that Congress did not intend FDA oversight to be the exclusive means of ensuring drug safety and effectiveness.

Wyeth v. Levine, 129 S. Ct. at 1200 (citations omitted).

CONCLUSION

The petition for a writ of certiorari should be denied.

July 30, 2010

Respectfully submitted,

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APPENDIX A:

United States Code Annotated

Title 21. Food and Drugs

FEDERAL FOOD DRUG AND COSMETIC ACT

§ 352. Misbranded Drugs and Devices

A drug or device shall be deemed to be misbranded—

* * *

(f) Directions for use and warnings on label

Unless its labeling bears . . .

(2) such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users . . . .

APPENDIX B:

21 C.F.R. § 201.57(e) (2005) - excerpt

Code of Federal Regulations

Title 21. Food and Drugs
Subtitle C: Drugs - General
Part 201. Labeling

§ 201.57. Specific requirements on content and format of labeling for human prescription drugs.

(e) Warnings.

Under this section heading, the labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved. . . .

* * *

APPENDIX C:

21 C.F.R. § 314.70(b) (2005) - excerpt

Code of Federal Regulations

Title 21. Food and Drugs
Subtitle D: Drugs for Human Use
Part 314. Applications for FDA Approval to Market a New Drug

§ 314.70. Supplements and other changes to an approved application.

(b) Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes).

(1) A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.

(2) These changes include, but are not limited to:

* * *

(v) The following labeling changes:

(A) Changes in labeling, except those described in paragraphs (c)(6)(iii), (d)(2)(ix), or (d)(2)(x) of this section;

* * *

(3) The applicant must obtain approval of a supplement from FDA prior to distribution of a drug product made using a change under paragraph (b) of this section.

* * *

(4) An applicant may ask FDA to expedite its review of a supplement for public health reasons or if a delay in making the change described in it would impose an extraordinary hardship on the applicant. Such a supplement and its mailing cover should be plainly marked: "Prior Approval Supplement-Expedited Review Requested."

* * *

APPENDIX D:

21 C.F.R. § 314.70(c)(6)(iii) (2005)

Code of Federal Regulations

Title 21. Food and Drugs
Subtitle D: Drugs for Human Use
Part 314. Applications for FDA Approval to Market a New Drug

§ 314.70. Supplements and other changes to an approved application.

(c) . . .

* * *

(6) The agency may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved application may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change. These changes include, but are not limited to: . . .

* * *

(iii) Changes in the labeling to accomplish any of the following:

(A) To add or strengthen a contraindication, warning, precaution, or adverse reaction;

(B) To add or strengthen a statement about drug abuse, dependence, psychological effect, or overdosage;

(C) To add or strengthen an instruction about dosage and administration that is

intended to increase the safe use of the drug product;

(D) To delete false, misleading, or unsupported indications for use or claims for effectiveness; or

(E) Any labeling change normally requiring a supplement submission and approval prior to distribution of the drug product that FDA specifically requests be submitted under this provision.

* * *

REPLY BRIEF

(4)

No. 09-1501

Supreme Court, U.S.
FILED
AUG 27 2010
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IN THE

Supreme Court of the United States

ACTAVIS, INC.,
Petitioner,

v.

JULIE DEMAHY,
Respondent.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Fifth Circuit

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REPLY BRIEF FOR PETITIONERS

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ARGUMENT

Petitioner seeks certiorari on the question, squarely presented by the decision of the Fifth Circuit, of whether the states are preempted by the Federal Food, Drug, and Cosmetic Act and Food and Drug Administration (FDA) regulations from requiring a manufacturer of a generic drug to add safety information to its label without FDA approval, where the brand drug has not changed its label. The issue is a purely legal question and one that requires this Court's swift intervention, so that generic drug companies may know whether they have unilateral authority to change their product labels, which the FDA had previously instructed was prohibited by federal law. Without this Court's intervention, generic drug companies will be forced to bear the cost of thousands of lawsuits, while waiting for courts to resolve the legal issue presented by Actavis's petition for certiorari, potentially forcing them to abandon their low-cost business model that has been the basis for tremendous healthcare savings in this country.

In her Opposition, Respondent offers barely any defense of the Fifth Circuit's holding that a generic drug manufacturer may make a unilateral change to its label through the "Changes Being Effected" (CBE) process, and she has chosen not to respond to Petitioner's argument that such a change is flatly prohibited by FDA's regulations. *See* Petition at 9-11. Instead, Respondent contends that certiorari should not be granted because a decision in this case would be an "advisory opinion." As we demonstrate below, however, a decision in this case favorable to Petitioner would not be advisory because

it will eliminate one of Respondent's discrete theories for liability, thus affecting the types of evidence that would be introduced at trial and potentially the outcome on remand. Because the issue presented is a purely legal question, there is no obstacle to deciding it now rather than waiting for the conclusion of trial and a final judgment.

I. A RULING PREVENTING RESPONDENT FROM PURSUING AN INVALID THEORY OF LIABILITY AT TRIAL IS NOT AN ADVISORY OPINION.

Although Respondent devotes considerable attention to the merits of the preemption issue in her Brief in Opposition, she offers little defense of the Fifth Circuit's holding that the manufacturer of a generic drug may unilaterally make changes to its label under the CBE regulation. As demonstrated in the petition in this case and the petitions and amicus brief filed in *Acatvis Elizabeth, LLC v. Mensing*, No. 09-1039 and *Pliva, Inc. v. Mensing*, No. 09-993, that holding was erroneous. Whether or not Respondent may proceed under other theories of liability – an issue presented in *Mensing* but not in this case – a decision by this Court precluding Respondent from relying on the CBE regulation will have a direct and dramatic effect on the trial of this case and the many other such cases pending across the country.

Respondent breezily contends that the petition should be denied because it asks the Court to render an "advisory opinion." Opp. at 7-9. The prohibition against advisory opinions is rooted in the Article III limitation on judicial power to "cases" or

"controversies." *See Aetna Life Ins. Co. v. Haworth*, 300 U.S. 227, 239 (1937). In order to be justiciable, there must be "a real and substantial controversy" admitting of "an immediate and definitive determination of the legal rights of the parties in an adversary proceeding." *Id.* at 241. The doctrine protects against determination of disputes that are of "a hypothetical or abstract character," "academic," or "moot." *Id.* at 240. This is not the circumstance here, where Petitioner and Respondent "remain adverse, and 'valuable legal rights . . . will be directly affected to a specific and substantial degree by the decision of the question of law.'" *Asarco Inc. v. Kadish*, 490 U.S. 605, 619 (1989).

Here, a decision reversing the Fifth Circuit's holding that a generic drug manufacturer may make unilateral label changes will directly and specifically affect the legal rights of Respondent and Petitioner in their ongoing litigation. If this Court holds that federal law prohibits a generic manufacturer from making a unilateral label change, Respondent will be unable to proceed on its theory that Petitioner had a duty to warn by changing its label prior to the time the brand had changed its label. Instead, Respondent will have to proceed on a completely different theory and to establish that Petitioner had a duty to seek permission from FDA to change its label, and that FDA would have approved that change. Petitioner's liability will be limited to this alternative theory, which is not described in her complaint below (App. 92a-112a), and Respondent will be required to make an entirely different factual showing at trial than would be required if she is permitted to proceed under the theory that Petitioner

may unilaterally change its label, including possibly presenting evidence on whether FDA would have granted a request for a label change.

The Fifth Circuit has already ruled against Respondent's claim that Actavis had a duty to communicate directly with physicians about the claimed risks of metoclopramide, absent prior FDA approval. App. 34a-35a. Respondent's primary theories will thus be eliminated, changing the evidence, jury instructions, and course of the entire trial. Review by this Court is appropriate where the decision "is fundamental to the further conduct of the case." *United States v. General Motors Corp.*, 323 U.S. 373, 377 (1945).

The only case cited by Respondent, *Herb v. Pitcairn*, 324 U.S. 117 (1945), does not support her advisory opinion argument. *See* Opp. at 8. *Herb* addresses the situation in which a challenge to one of several alternative rulings would not have affected the final judgment. 324 U.S. at 125-26. In that case, the Supreme Court decided to seek clarification from the state court as to whether the final judgment rested – independently and in total – on a state law ground, such that a decision on the issue of federal law could not have changed the judgment or afforded any relief to the petitioner. In such a case, providing an opinion on that point of federal law is advisory because it affects nothing between the parties below. In the present case, as explained above, the alternative theories of liability lead to very different proceedings in the lower court and potentially to a different result. While Respondent's failure to warn claim may survive even if this Court rules in

Petitioner's favor, the primary theory of liability will be preempted and Respondent will have a much more difficult time proving her case.

Just as reviewing the decision on a motion to exclude evidence is appropriate because it raises an important issue regarding the conduct of the upcoming trial, *see Oliver v. United States*, 466 U.S. 170 (1984), so too will a decision in this case provide clarity on an important legal issue and narrow the issues for trial. The question in this case is one of pure law, involving interpretation of statutes and FDA regulations, and Respondent has not pointed to any factual development that could possibly clarify the issue any further. Indeed, this case is comparable to *Weyhrauch v. United States*, 130 S. Ct. 2971 (2010) (remanded for further consideration in light of the decision in *Skilling v. United States*, 130 S. Ct. 2896 (2010)), where the Court granted certiorari last term on a question related to just one particular theory of honest services fraud. *See Weyhrauch v. United States*, 129 S. Ct. 2863 (2009) (granting petition for writ of certiorari). Even if the Court had resolved the question presented in that case against the government, the honest services fraud prosecution still could be pursued under a different theory. *See United States v. Weyhrauch*, 548 F.3d 1237, 1247 (9th Cir. 2008) (noting that the allegations could support an alternative theory of honest services fraud). That is exactly the situation here, where this Court's decision will resolve the most important theory, although it may not dispose entirely of Respondent's case. The fact that a claim may go forward on a very different theory does not make a decision "advisory."

II. THE ISSUE IS IMPORTANT AND MERITS IMMEDIATE REVIEW EITHER ALONE OR IN CONJUNCTION WITH *MENSING*.

The Fifth Circuit's holding that generic drug manufacturers are allowed to make unilateral label changes has national importance. The decision effectively imposes severe financial obligations on generic drug manufacturers nationwide because of the risk of liability in a court in the Fifth Circuit. Under the system designed by Congress, generic companies are not required to conduct clinical trials or to engage in the difficult and expensive work of monitoring and analyzing the information to determine if a labeling change is appropriate. If the Fifth Circuit's decision stands, new litigation and other costs may be imposed on generic companies by state law, which may diminish the ability of generic companies to provide a low cost product to consumers. This petition presents an issue of great importance, and a purely legal question, that can and should be resolved now. This issue can be resolved on its own, or in conjunction with the petitions in *Mensing*, which raise closely related questions.*

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* On May 24, 2010, the Court requested the Solicitor General's views in *Mensing*, which also raises the legal issue Petitioners have urged this Court to decide. Accordingly, Petitioners respectfully request that the Court consider the *Mensing* and *Demahy* petitions at the same time.

Respectfully submitted.

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JOINT APPENDIX

Supreme Court, U.S.
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Nos. 09-993 vide 09-1039, 09-1501

In the Supreme Court of the United States

PLIVA, Inc., et al., 09-993 vide 09-1039, *Petitioners*,

v.

Gladys Mensing, *Respondent*.

Actavis Elizabeth, LLC, 09-1039 vide 09-993, *Petitioner*,

v.

Gladys Mensing, *Respondent*.

Actavis, Inc., 09-1501, *Petitioner*,

v.

Julie Demahy, *Respondent*.

On Writs of Certiorari to the United States Courts of Appeals for the Fifth and Eighth Circuits

JOINT APPENDIX, Volume 1

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Notice of Removal, Jury Trial Requested, filed June 2, 2008 ..... JA 449

Answer of Defendant Actavis, Inc., Jury Trial Demanded, filed June 6, 2008 ..... JA 458

Order and Reasons of the U.S. District Court, Eastern District of Louisiana, filed October 28, 2008 ..... JA 477

Opinion of Fifth Circuit Court of Appeals, filed January 8, 2010 ..... JA 520

RELEVANT DOCKET ENTRIES

United States District Court for the District of Minnesota

No. 07-cv-03919-DWF

Mensing v. Wyeth, Inc., et al.

Date Filed	#	Docket Text
09/07/2007	1	COMPLAINT against all defendants (Filing fee $ 350 receipt number 40016011.) assigned to Judge Patrick J Schiltz per Master List referred to Magistrate Judge Raymond L Erickson., filed by Gladys Mensing. (Attachments: # 1 Complaint part 2# 2 Civil Cover Sheet) (jdf) QC'd by gjs. (Entered: 09/07/2007)
11/13/2007	6	ANSWER to Complaint with Jury Demand by Actavis Elizabeth, LLC. (Attachments: # 1 Certificate of Service) (Hutchens, Michael) (Entered: 11/13/2007)
02/19/2008	39	MOTION to Dismiss by Actavis Elizabeth, LLC. (Lindeman, Bradley) (Entered: 02/19/2008)
02/19/2008	41	MEMORANDUM in Support re 39 MOTION to Dismiss filed by Actavis Elizabeth, LLC. (Attachments: # 1 LR7.1 Word Count Compliance Certificate) (Lindeman, Bradley) (Entered: 02/19/2008)

Date Filed	#	Docket Text
02/19/2008	42	AFFIDAVIT of Bradley J. Lindeman in SUPPORT OF 39 MOTION to Dismiss filed by Actavis Elizabeth, LLC. (Attachments: # 1 Exhibit(s) A & B, # 2 Exhibit(s) C & D, # 3 Exhibit(s) E & F, # 4 Exhibit(s) G)(Lindeman, Bradley) (Entered: 02/19/2008)
02/22/2008	48	AMENDED COMPLAINT against all defendants, filed by Gladys Mensing. (Johnson, Michael) (Entered: 02/22/2008)
03/11/2008	52	ANSWER to Amended Complaint by Actavis Elizabeth, LLC. (Attachments: # 1 Certificate of Service) (Lindeman, Bradley) (Entered: 03/11/2008)
03/13/2008	54	*DEFENSES, JURY DEMAND AND* ANSWER to Amended Complaint by Pliva, Inc.. (Attachments: # 1 Certificate of Service)(Lenahan, Dana) (Entered: 03/13/2008)
03/13/2008	55	ANSWER to Amended Complaint by Teva Pharmaceuticals USA, Inc.. (Attachments: # 1 Certificate of Service) (Hashmall, David) (Entered: 03/13/2008)
03/13/2008	56	ANSWER to Amended Complaint by UDL Labortories, Inc.. (Attachments: # 1 Certificate of Service) (Hashmall, David) (Entered: 03/13/2008)
03/25/2008	64	MOTION to Dismiss *or for Summary Judgment* by Pliva, Inc..

Date Filed	#	Docket Text
		(Lenahan, Dana) (Entered: 03/25/2008)
03/25/2008	66	MEMORANDUM in Support re 64 MOTION to Dismiss *or for Summary Judgment* filed by Pliva, Inc.. (Attachments: # 1 LR7.1 Word Count Compliance Certificate) (Lenahan, Dana) (Entered: 03/25/2008)
03/25/2008	67	AFFIDAVIT of Tiffany Reece Clark in SUPPORT OF 64 MOTION to Dismiss *or for Summary Judgment* filed by Pliva, Inc.. (Attachments: # 1 Exhibit(s) A-1, # 2 Exhibit(s) A-2, # 3 Exhibit(s) B-1, # 4 Exhibit(s) B-2, # 5 Exhibit(s) B-3, # 6 Exhibit(s) B-4, # 7 Exhibit(s) C-1, # 8 Exhibit(s) C-2, # 9 Exhibit(s) C-3, # 10 Exhibit(s) C-4, # 11 Exhibit(s) D, # 12 Exhibit(s) E, # 13 Exhibit(s) F, # 14 Exhibit(s) G, # 15 Exhibit(s) H-1, # 16 Exhibit(s) H-2, # 17 Exhibit(s) H-3, # 18 Exhibit(s) H-4, # 19 Exhibit(s) I, # 20 Exhibit(s) J, # 21 Exhibit(s) K-1, # 22 Exhibit(s) K-2, # 23 Exhibit(s) K-3, # 24 Exhibit(s) K-4, # 25 Exhibit(s) K-5, # 26 Exhibit(s) L-1, # 27 Exhibit(s) L-2, # 28 Exhibit(s) L-3, # 29 Exhibit(s) L-4, # 30 Exhibit(s) L-5, # 31 Exhibit(s) M-1, # 32 Exhibit(s) M-2, # 33 Exhibit(s) M-3, # 34 Exhibit(s) M-4, # 35 Exhibit(s) N, # 36 Exhibit(s) O, # 37 Exhibit(s) P, # 38 Exhibit(s) Q, # 39 Exhibit(s) R, #

Date Filed	#	Docket Text
		40 Exhibit(s) S, # 41 Exhibit(s) T, # 42 Exhibit(s) U, # 43 Exhibit(s) V)(Lenahan, Dana) (Entered: 03/25/2008)
03/25/2008	68	Declaration of Nicholas Tantillo in Support of 64 MOTION to Dismiss *or for Summary Judgment* filed by Pliva, Inc.. (Attachments: # 1 Exhibit(s) 1-31, part 1, # 2 Exhibit(s) 1-31, part 2, # 3 Exhibit(s) 1-31, part 3, # 4 Exhibit(s) 1-31, part 4, # 5 Exhibit(s) 1-31, part 5, # 6 Exhibit(s) 1-31, part 6, # 7 Exhibit(s) 1-31, part 7)(Lenahan, Dana) (Entered: 03/25/2008)
04/21/2008	71	MEMORANDUM in Opposition re 64 MOTION to Dismiss *or for Summary Judgment*, 39 MOTION to Dismiss filed by Gladys Mensing. (Attachments: # 1 LR7.1 Word Count Compliance Certificate) (Johnson, Michael) (Entered: 04/21/2008)
04/21/2008	72	AFFIDAVIT of Michael K. Johnson in OPPOSITION TO 64 MOTION to Dismiss *or for Summary Judgment*, 39 MOTION to Dismiss filed by Gladys Mensing. (Attachments: # 1 Exhibit(s) Exhibit 1, # 2 Exhibit(s) Exhibit 2, # 3 Exhibit(s) Exhibits 3-11, # 4 Exhibit(s) Exhibits 12-14, # 5 Exhibit(s) Exhibits 15-17, # 6 Exhibit(s) Exhibit 18, part 1, # 7

Date Filed	#	Docket Text
		Exhibit(s) Exhibit 18, part 2, # 8 Exhibit(s) Exhibits 19-22, # 9 Exhibit(s) Exhibits 23-25, # 10 Exhibit(s) Exhibit 26, # 11 Exhibit(s) Exhibit 27)(Johnson, Michael) (Entered: 04/21/2008)
04/28/2008	77	REPLY re 71 Memorandum in Opposition to Motion filed by Pliva, Inc.. (Attachments: # 1 LR7.1 Word Count Compliance Certificate) (Lenahan, Dana) (Entered: 04/28/2008)
04/28/2008	78	Second AFFIDAVIT of Tiffany Reece Clark in SUPPORT OF 64 MOTION to Dismiss *or for Summary Judgment* filed by Pliva, Inc.. (Attachments: # 1 Exhibit(s) AA, # 2 Exhibit(s) BB, # 3 Exhibit(s) CC, # 4 Exhibit(s) DD, # 5 Exhibit(s) EE-1, # 6 Exhibit(s) EE-2, # 7 Exhibit(s) EE-3, # 8 Exhibit(s) EE-4, # 9 Exhibit(s) FF-1, # 10 Exhibit(s) FF-2, # 11 Exhibit(s) GG-1, # 12 Exhibit(s) GG-2, # 13 Exhibit(s) GG-3, # 14 Exhibit(s) HH)(Lenahan, Dana) (Entered: 04/28/2008)
06/17/2008	86	ORDER granting 39 Motion to Dismiss; granting 64 Motion to Dismiss; denying 85 Motion to Strike; and denying Plaintiff's Rule 56(f) Motion. This action is dismissed as to Defendants Actavis and Pliva (Written Opinion).Signed by Judge Donovan W. Frank on

Date Filed	#	Docket Text
		6/17/08. (GMO) (Entered: 06/17/2008)
07/03/2008	87	MOTION for Summary Judgment by UDL Labortories, Inc., Teva Pharmaceuticals USA, Inc.. (Hashmall, David) (Entered: 07/03/2008)
07/03/2008	89	MEMORANDUM in Support re 87 MOTION for Summary Judgment filed by UDL Labortories, Inc., Teva Pharmaceuticals USA, Inc.. (Hashmall, David) (Entered: 07/03/2008)
07/03/2008	91	AFFIDAVIT of Philip Erickson in SUPPORT OF 87 MOTION for Summary Judgment filed by UDL Labortories, Inc., Teva Pharmaceuticals USA, Inc.. (Hashmall, David) (Entered: 07/03/2008)
07/03/2008	92	AFFIDAVIT of Timothy G. Wait in SUPPORT OF 87 MOTION for Summary Judgment filed by UDL Labortories, Inc., Teva Pharmaceuticals USA, Inc.. (Hashmall, David) (Entered: 07/03/2008)
09/04/2008	115	MEMORANDUM in Opposition re 103 Joint MOTION to Dismiss *Defendants Alpharma Inc. and Purepac Pharmaceutical Co.*, 87 MOTION for Summary Judgment, 110 MOTION for Summary Judgment *Pursuant to Fed. R. Civ. P. 56(c)* filed by Gladys Mensing.

Date Filed	#	Docket Text
		(Attachments: # 1 LR7.1 Word Count Compliance Certificate, # 2 Certificate of Service)(Johnson, Michael) (Entered: 09/04/2008)
09/12/2008	121	REPLY re 87 MOTION for Summary Judgment filed by UDL Labortories, Inc., Teva Pharmaceuticals USA, Inc.. (Attachments: # 1 Certificate of Compliance with LR 37.1, # 2 Certificate of Service)(Hashmall, David) (Entered: 09/12/2008)
10/27/2008	137	MEMORANDUM OPINION AND ORDER granting 87 Motion for Summary Judgment; granting 96 Motion for Summary Judgment; granting 110 Motion for Summary Judgment (Written Opinion). Signed by Judge Donovan W. Frank on 10/24/08. (GMO) (Entered: 10/27/2008)
10/28/2008	138	JUDGMENT (Attachments: # 1 Civil Notice - appeal, # 2 Civil-8th Circuit Pre-Hearing Conference Notice)(RLR) (Entered: 10/28/2008)
10/30/2008	139	AMENDED MEMORANDUM OPINION AND ORDER (Written Opinion). Signed by Judge Donovan W. Frank on 10/30/08. (GMO) (Entered: 10/30/2008)
11/26/2008	142	NOTICE OF APPEAL TO 8TH CIRCUIT as to 139 Memorandum & Opinion, 138 Judgment by Gladys Mensing. (Attachments: # 1 COA - Form A, # 2 Affidavit of

Date Filed	#	Docket Text
		Service)(LPH) QC'd by KT on 12/2/08. (KT) (Entered: 11/26/2008)
02/20/2009	149	Subsequent NOTICE OF APPEAL transcripts docket #147 dated 1/7/09 and 141 dated 11/21/08 sent to the Court of Appeals. (VEM) (Entered: 02/20/2009)
11/27/2009	151	Opinion of USCA re: we reverse the judgment in favor of the generic manufacturers but affirm the judgment as to the name brand manufacturers, as to 142 Notice of Appeal to 8th Circuit filed by Gladys Mensing. (Attachments: # 1 Cover Letter)(jam) (Entered: 12/02/2009)
11/27/2009	152	USCA JUDGMENT re: it is hereby ordered and adjudged that the judgment of the district court in this cause is affirmed in part and reversed in part in accordance with the opinion of this Court, as to 142 Notice of Appeal to 8th Circuit filed by Gladys Mensing (received electronically from COA). (jam) (Entered: 12/02/2009)
12/18/2009	153	MANDATE of USCA re: the formal mandate is hereby issued in the above-styled matter, as to 142 Notice of Appeal to 8th Circuit filed by Gladys Mensing (received electronically from COA). (jam) (Entered: 12/22/2009)

General Docket
Eighth Circuit Court of Appeals

Court of Appeals Docket #: 08-3850

Mensing v. Wyeth, Inc., et al.

12/10/2008 Civil case docketed. [3497620] [08-3850] (CYZ)

12/10/2008 Originating court document filed consisting of notice of appeal, memorandum opinion and order dated 10/24/08, judgment of 10/28/08, district court docket entries link, [3497697] [08-3850] (CYZ)

02/20/2009 BRIEF FILED - APPELLANT BRIEF filed by Gladys Mensing, w/service 02/19/2009, 70 PDF pages, w/Addendum 10 copies. Words/lines/pages 57 pages. Brief of Actavis Elizabeth, LLC, Alpharma, Pliva, Inc., Purepac Pharmaceutical Company, Schwarz Pharma, Inc., Teva Pharmaceuticals USA, Inc., UDL Laboratories, Inc. and Wyeth due on 03/23/2009 [3519146] [08-3850] (LAB)

02/23/2009 RECORD FILED - Record Part: MOTION TRANSCRIPT, No. of Volumes: 1, Volumes Location: STP, Source Location: DC, Dt. of Proceeding/Hearing: 05/09/2008, No. of Pgs.: 68, Court Reporter: Anderson, Jeanne; Record Part: MOTION TRANSCRIPT, No. of Volumes: 1, Volumes Location: STP, Source

Location: D.C., Dt. of Proceeding/Hearing: 09/24/2008, No. of Pgs.: 76, Court Reporter: Anderson, Jeanne [3519088] [08-3850] (CYZ)

02/23/2009 RECORD FILED - Record Part: APLNT/PET APPENDIX, No. of Volumes: 3, Volumes Location: St. Louis, Comments: 3 copies [3519159] [08-3850] (LAB)

04/27/2009 BRIEF FILED - APPELLEE BRIEF filed by Actavis Elizabeth, LLC, w/service 04/24/2009, 62 PDF pages, No Addendum, 10 copies. Words/lines/pages 11,641 words. [3541098] [08-3850] (LAB)

04/27/2009 RECORD FILED - Record Part: APLEE/RES (Actavis Elizabeth, LLC) APPENDIX, No. of Volumes: 2, Volumes Location: St. Louis, Comments: 3 copies [3541104] [08-3850] (LAB)

04/27/2009 BRIEF FILED - APPELLEE BRIEF filed by Pliva, Inc., Teva Pharmaceuticals USA, Inc. and UDL Laboratories, Inc., w/service 04/24/2009, 84 PDF pages, w/Addendum 10 copies. Words/lines/pages 17,156 words. [3541589] [08-3850] (LAB)

04/27/2009 RECORD FILED - Record Part: APLEE/RES APPENDIX (Pliva, Inc.; Teva Pharmaceuticals, USA, Inc.; and UDL Laboratories, Inc.), No. of Volumes: 3, Volumes Location: St. Louis, Comments: 3 copies [3541595] [08-3850] (LAB)

05/18/2009	BRIEF FILED - APPELLANT REPLY BRIEF filed by Gladys Mensing, w/service 05/11/2009, 47 PDF pages, w/Addendum 10 copies. Words/ lines/pages 9,996 words. [3548669] [08-3850] (LAB)
05/18/2009	RECORD FILED - Record Part: SUPPLEMENTAL APNDX, No. of Volumes: 1, Volumes Location: St. Louis, Comments: 3 copies [3548671] [08-3850] (LAB)
10/01/2009	28(j) citation filed by Appellee Teva Pharmaceuticals USA, Inc. w/service 10/01/2009 - FOR CAL. [3591363] [08-3850] (DLH)
10/02/2009	28(j) citation filed by Appellee Actavis Elizabeth, LLC w/service 10/02/2009 - FOR CAL. [3591657] [08-3850] (RAD)
10/07/2009	28(j) citation filed by Appellee Pliva, Inc. w/service 10/07/2009 - FOR CAL. [3593219] [08-3850] (LEM)
10/08/2009	28(j) citation filed by Appellant Gladys Mensing w/service 10/08/2009 - FOR CAL. [3593761] [08-3850] (LMB)
10/20/2009	ARGUED & SUBMITTED in St. Paul to Judges Roger L. Wollman, Diana E. Murphy, Kermit E. Bye. Mr. Louis M. Bograd for Appellant Gladys Mensing, Mr. Henninger S. Bullock for Appellees Schwarz Pharma, Inc. and Wyeth, and Mr. Joseph Paul Thomas for Appellee PLIVA, Inc. Rebuttal by Mr. Louis M.

	Bograd for Gladys Mensing. RECORDED [3597291] [08-3850] (CBC)
11/06/2009	28(j) citation filed by Appellant Gladys Mensing w/service 11/06/2009 - FOR CAL. [3603546] [08-3850] (LMB)
11/13/2009	Response of Appellee Pliva, Inc. to 28(j) citation, [3603546-2], filed by Gladys Mensing in 08-3850 w/service 11/13/2009 - FOR CAL. [Modified by CBC][3605100] [08-3850] (JPT)
11/16/2009	28(j) citation filed by Appellant Gladys Mensing w/service 11/16/2009 - FOR CAL. [3605691] [08-3850] (CPP)
11/27/2009	OPINION FILED - THE COURT: ROGER L. WOLLMAN, DIANA E. MURPHY and KERMIT E. BYE. Diana E. Murphy, Authoring Judge (PUBLISHED) [3609541] [08-3850] (DMS)
11/27/2009	JUDGMENT FILED - The judgment of the originating court is AFFIRMED in part and REVERSED in part in accordance with the opinion. ROGER L. WOLLMAN, DIANA E. MURPHY and KERMIT E. BYE Hrg Oct 2009 [3609552] [08-3850] (DMS)
12/18/2009	MANDATE ISSUED. [3617027] [08-3850] (PAW)

IN THE UNITED STATES DISTRICT COURT
District of Minnesota

CASE NO. 07 CV 3919
PJS/RLE

[Filed September 7, 2007]

Gladys Mensing,

v.

WYETH, INC. (d/b/a WYETH); SCHWARZ PHARMA, INC.; PLIVA, INC.; TEVA PHARMACEUTICALS, USA, INC.; ALPHARMA, INC., d/b/a ALPHARMA PHARMACEUTICALS; UDL LABORATORIES, INC.; ACTAVIS ELIZABETH, LLC, and PUREPAC PHARMACEUTICAL CO., and the following fictitious party defendants (whether singular or plural, individual or corporate): No. 1, that entity which originally obtained permission from the U.S. Food and Drug Administration to market the drug branded Reglan; No. 2, that entity which obtained permission from the FDA to market the Reglan, metoclopramide and/or metoclopramide HCl ingested by Gladys Mensing; No. 3, that entity which originally manufactured and sold any Reglan which was ultimately ingested by Gladys Mensing; No. 4, that entity which originally manufactured and sold any Reglan, metoclopramide and/or metoclopramide HCl which was ultimately ingested by Gladys Mensing; No. 5, that entity which marketed

Reglan or generic metoclopramide and/or metoclopramide HCl.	)
Defendants.	)

COMPLAINT FOR DAMAGES
DEMAND FOR JURY TRIAL.

Gladys Mensing, Plaintiff, by and through her undersigned attorneys, state and allege as follows:

I. PARTIES

1. Gladys Mensing, Plaintiff, (hereinafter referred to as "Plaintiff") is an individual of the full age of majority who is a resident and citizen of Steele County, State of Minnesota.

2. Plaintiff brings this action for the purpose of recovering all damages allowable by law for personal injuries she suffered as a result the ingestion of Reglan, metoclopramide and/or metoclopramide HCl.

3. Defendant, Wyeth, Inc., d/b/a Wyeth (hereinafter "Wyeth") is a Delaware corporation with its principal place of business at 5 Giralda Farms, Madison, New Jersey 07940.

4. References in this Complaint to "Wyeth" include individually and collectively all divisions and/or subsidiaries, Wyeth as successor in interest to A.H. ROBINS, INC., AMERICAN HOME Drugs CORPORATION, and ESI.

5. At all times material hereto, Wyeth was engaged in the business of testing, developing, manufacturing, labeling, marketing, distributing, promoting and/or selling, either directly or indirectly, through third parties, as successor in interest, or other related entities, Reglan, metoclopramide and/or metoclopramide HCl tablets in the State of Minnesota and in interstate commerce. Wyeth may be served with process through its registered agent, Corporation Service Company, 2711 Centerville Road, Suite 400, Wilmington, DE 19808. Wyeth is subject to the jurisdiction and venue of this Court.

6. Wyeth manufactures and distributes generic metoclopramide through its ownership of ESI Ledule, Inc. (a former subsidiary which merged into Wyeth).

7. Defendant, Schwarz Pharma, Inc., (hereinafter "Schwarz") is a Delaware corporation, duly qualified to do business in the State of Minnesota with its principal place of business in Mequon, Wisconsin.

8. Defendant Schwarz and/or one of its predecessors in interest and/or one of its family of wholly owned divisions was engaged in the business of testing, developing, manufacturing, labeling, marketing, distributing, promoting and/or selling, either directly or indirectly, through third parties, as successor in interest, or other related entities, Reglan, metoclopramide and/or metoclopramide HCl tablets in the State of Minnesota and in

interstate commerce. Schwarz may be served with process through its registered agent, CSC Entity Services, LLC, 103 Foulk Road, Suite 200, Wilmington, Delaware 19803. Schwarz Pharma, Inc. is subject to the jurisdiction and venue of this Court.

9. The Defendant, PLIVA USA, Inc., (hereinafter "PLIVA") is a New York corporation with its principal place of business in New Jersey.

10. At all times material hereto, PLIVA was engaged in the business of testing, developing, manufacturing, labeling, marketing, distributing, promoting and/or selling, either directly or indirectly, through third parties or related entities, Reglan, metoclopramide and/or metoclopramide HCl tablets in the State of Minnesota and in interstate commerce. PLIVA may be served with process through its agent for service of process at Corporation Trust Company, 820 Bear Tavern Road, 3rd Floor, West Trenton, NJ 08628. PLIVA is subject to the jurisdiction and venue of this Court.

11. The Defendant, Teva Pharmaceuticals, USA, Inc., (hereinafter "Teva") is a Delaware corporation with its principal place of business in Pennsylvania. At all times material hereto, Teva was engaged in the business of testing, developing, manufacturing, labeling, marketing, distributing, promoting and/or selling, either directly or indirectly, through third parties or related entities, Reglan, metoclopramide and/or metoclopramide HCl tablets in the State of Minnesota and in interstate commerce. Teva

may be served with process through its registered agent, the Corporation Trust Company, located at Corporation Trust Center, 1209 Orange Street, Wilmington, DE 19801. Teva is subject to the jurisdiction and venue of this Court.

12. The Defendant, Alpharma Inc., d/b/a Alpharma Pharmaceuticals (hereinafter "Alpharma"), is a Delaware Corporation and is the parent corporation of Purepac Pharmaceutical Co., which at all times pertinent hereto manufactured and distributed the generic drug metoclopramide and/or metoclopramide HCl.

13. At all times material hereto, Alpharma was engaged in the business of testing, developing, manufacturing, labeling, marketing, distributing, promoting and/or selling, either directly or indirectly, through third parties or related entities, Reglan, metoclopramide and/or metoclopramide HCl tablets in the State of Minnesota and in interstate commerce. Alpharma is subject to the jurisdiction and venue of this Court. Alpharma may be served with process through its agent for service: Corporation Service Company, 2711 Centerville Road, Suite 400, Wilmington, Delaware 19809.

14. The Defendant, Purepac Pharmaceutical Co. (hereinafter "Purepac"), is a New Jersey Corporation. At all times material hereto, Purepac was engaged in the business of testing, developing, manufacturing, labeling, marketing, distributing, promoting and/or selling, either directly or indirectly, through third parties or

related entities, Reglan, metoclopramide and/or metoclopramide HCl tablets in the State of Minnesota and in interstate commerce. Purepac may be served with process through its corporate headquarters, 1 Executive Drive, Fort Lee, New Jersey 07024-3309. Purepac is subject to the jurisdiction and venue of this Court.

15. The Defendant, UDL Laboratories, Inc., is an Illinois Corporation. At all times material hereto, UDL was engaged in the business of testing, developing, manufacturing, labeling, marketing, distributing, promoting and/or selling, either directly or indirectly, through third parties or related entities, Reglan, metoclopramide and/or metoclopramide HCl tablets in the State of Minnesota and in interstate commerce. UDL Laboratories, Inc., may be served with process through its agent for process: Illinois Corporation Service, 801 ADLAI Stevenson Drive, Springfield, Illinois 62703. UDL Laboratories, Inc., is subject to the jurisdiction and venue of this Court.

16. The Defendant, Actavis Elizabeth, LLC, (hereinafter "Actavis"), is a New Jersey Corporation. At all times material hereto, Actavis was engaged in the business of testing, developing, manufacturing, labeling, marketing, distributing, promoting and/or selling, either directly or indirectly, through third parties or related entities, Reglan/metoclopramide and/or metoclopramide HCl tablets in the State of Minnesota and in interstate commerce. Actavis is subject to the jurisdiction and venue of this Court.

17. Fictitious parties No. 1 through 6 are party Defendants the identities of whom or which is otherwise known to Plaintiff at this time, but, whose true names will be substituted by amendment when the aforesaid lacking knowledge is ascertained.

18. All Defendants, identified *supra,* inclusive, and each of them, may be referred to in this complaint collectively as "THE DRUG COMPANY DEFENDANTS."

19. At all relevant times, DRUG COMPANY DEFENDANTS were acting by and through their agents, servants and/or employees, each of whom were acting within the scope and course of their employment by agency or authority on their behalf.

20. At all times relevant hereto, DRUG COMPANY DEFENDANTS were in the business of researching, designing, formulating, compounding, testing, manufacturing, producing, processing, assembling, inspecting, distributing, marketing, labeling, promoting, packaging and/or advertising the pharmaceutical drugs known as "Reglan", metoclopramide HCl and/or metoclopramide in the State of Minnesota and in interstate commerce.

21. At all relevant times, DRUG COMPANY DEFENDANTS did manufacture, create, design, assemble, test, label, sterilize, package, distribute, promote, supply, market, sell, advertise, and/or otherwise distribute in the

State of Minnesota and in interstate commerce Reglan and/or metoclopramide tablets.

22. At all relevant times, DRUG COMPANY DEFENDANTS sold, delivered and/or distributed such drugs for ultimate sale and/or use interstate commerce within the United States and the State of Minnesota by foreseeable users, including Plaintiff.

II. VENUE AND JURISDICTION

23. The venue of this action is proper because Plaintiff is a resident of the State of Minnesota and the acts of negligence occurred in the State of Minnesota.

24. DRUG COMPANY DEFENDANTS conducted business in the State of Minnesota through pharmaceutical sales representatives conducting business in the State of Minnesota on behalf of Defendants and because Defendants were engaged in testing, developing, manufacturing, labeling, marketing, distributing, promoting and/or selling, either directly or indirectly, through third parties or related entities tablets known as Reglan, metoclopramide HCL and/or metoclopramide; thus, there exists a sufficient nexus between the DRUG COMPANY DEFENDANTS' forum contacts and the Plaintiff's claims to justify assertion of jurisdiction in Minnesota.

III. FACTUAL BACKGROUND OF PLAINTIFF'S CLAIMS

25. During all material times, Gladys Mensing, (hereinafter referred to as "Plaintiff") was domiciled in the State of Minnesota.

26. On or about March 23, 2001, Plaintiff's physician prescribed Reglan at a dosage of 5 mg, b.i.d., to treat Plaintiff's diabetic gastroparesis.

27. The active ingredient, metoclopramide and metoclopramide HCl is a dopamine antagonist.

28. Subsequently, Plaintiff's physician increased Plaintiff's dosage to 10 mg to be taken four (4) times a day.

29. Subsequently, Plaintiff's physician increased the dosage of Plaintiff's prescription for Reglan, metoclopramide, and/or metoclopramide HCl, and prescribed it to Plaintiff for several years thereafter.

30. Upon information and belief, in prescribing the Reglan, metoclopramide, and/or metoclopramide HCl drugs to Plaintiff on a long-term basis, Plaintiff's physicians relied upon information published in the package inserts and/or the Physician's Desk Reference (hereinafter "PDR") or otherwise disseminated by the Reference Listed Drug Company (hereinafter "RLD") and/or the New Drug Application Holder (hereinafter "NDA holder"), in particular, that

information disseminated by Defendants Wyeth and Schwarz.

31. Plaintiff ingested Reglan, metoclopramide and/or metoclopramide HCl, as prescribed.

32. Plaintiff's long term ingestion of Reglan, metoclopramide and/or metoclopramide HCl caused her injuries.

33. Plaintiff's physicians were not aware of information different from or contrary to the inaccurate, misleading, materially incomplete, false and/or otherwise inadequate information disseminated in the PDR.

34. Wyeth and Schwarz, as the RLD and/or NDA holders, provided misleading information about the true risks associated with the use of Reglan, metoclopramide, and/or metoclopramide HCl to the medical community, Plaintiff's Physician, and Plaintiff (and other foreseeable users similarly situated).

35. On or about March of 2005, Plaintiff was taken to Plaintiff's physician, who discontinued Plaintiff's Reglan, metoclopramide, and/or metoclopramide HCl prescription due to the clinical presentation of lip smacking and tongue thrusting movements.

36. On or about September of 2005, Plaintiff was examined by Dr. Bruce A. Evans, Department of Neurology, Mayo Clinic, who diagnosed her as suffering from drug induced Tardive Dyskinesia

related to her long-term use of Reglan, metoclopramide, and/or metoclopramide HCl.

37. Plaintiff used the pharmaceutical drugs Reglan, metoclopramide, and/or metoclopramide HCl without substantial change in condition of the drugs between the time of design and manufacture of the drugs and the time Plaintiff used the drugs as directed.

38. Plaintiff's use of Reglan, metoclopramide, and/or metoclopramide HCl drugs, as prescribed, resulted in overexposure to the drugs Reglan, metoclopramide, and/or metoclopramide HCl which caused Plaintiff to suffer serious, permanent and disabling injuries, including but not limited to injuries of or associated with the central nervous and extrapyramidal motor systems, specifically Tardive Dyskinesia, a severe and often permanent disfiguring neurological movement disorder.

39. Plaintiff's serious and permanent injuries, as described above, came about as a foreseeable and proximate result of the RLD and/or NDA holder and the ANDA holders dissemination of inaccurate, misleading, materially incomplete, false, and otherwise inadequate information concerning the potential effects of exposure to Reglan, metoclopramide, and/or metoclopramide HCl and the ingestion of Reglan, metoclopramide, and/or metoclopramide HCl drug to the medical community, physicians, Plaintiff's physician, Plaintiff and other foreseeable users of the drug.

40. Use of Reglan, metoclopramide, and/or metoclopramide HCl caused Plaintiff to suffer serious, permanent and disabling injuries including but not limited to injuries of or associated with the central nervous and extrapyramidal motor systems.

41. Plaintiff has experienced and will continue to experience medical and related expenses, loss of ability to provide household services, disfigurement, disability, pain and suffering, psychological injury and other injuries and damages due to the injuries she suffered caused by the ingestion of this drug.

IV. ALLEGATIONS

42. Tardive dyskinesia is a debilitating neurological disorder that often results in involuntary and uncontrollable movements of the head, neck, face, arms, legs and trunk in addition to grotesque facial grimacing and open-mouthed, uncontrollable tongue movements, tongue thrusting, tongue chewing, and other involuntary movements.

43. Presently, there is no cure for tardive dyskinesia.

44. Plaintiff's condition is permanent.

45. Wyeth is the successor in interest to A.H. Robins Company, Inc., a Virginia corporation which first obtained approval by the United States Food and Drug Administration (hereinafter "FDA") to distribute

metoclopramide, under the brand name "Reglan" under the FDA's New Drug Application (NDA)[1] schema.

46. Under the FDA schema, Wyeth was/is the Reference Listed Drug Company (RLD), under a specific NDA, for Reglan, metoclopramide and metoclopramide HCl.

47. Wyeth knew that it must fully, truthfully and accurately disclose and communicate material safety data and information regarding a new drug's chemistry, proposed manufacturing process, proposed model labeling which includes warnings about risks and side effects, test results for the drug, results of animal studies, results of clinical studies and the drug's bioavailability, because the data and information would be relied upon by the medical community, physicians, Plaintiff's physician, Plaintiff and other like foreseeable users of Reglan, metoclopramide and metoclopramide HCl once the NDA was approved and Wyeth was listed as the Reference Listed Drug Company for Reglan, metoclopramide and metoclopramide HCl.

48. Wyeth failed to fully, truthfully and accurately communicate the risks of Reglan, metoclopramide and metoclopramide HCl, and as a result intentionally and fraudulently

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[1] Upon information and belief, Plaintiff believes Wyeth to be the holder of multiple NDAs' for Reglan, metoclopramide and metoclopramide HCl.

mislead the medical community, physicians, Plaintiff's physician and Plaintiff about the risks associated with long term use of metoclopramide.

49. Wyeth had a duty to ensure its warnings to the medical community are accurate and adequate; has a duty to conduct safety surveillance of adverse events for the drug, and to report *any* data related to the safety and/or accuracy of the warnings and information disseminated regarding the drug.

50. Wyeth knowingly, intentionally and negligently disseminated misleading information to physicians' across the country, through a publication known as the *Physicians' Desk Reference*, labeling information for Reglan, metoclopramide and metoclopramide HCl which mislead the medical community, physicians and Plaintiff's physician about the risks of long term ingestion of the drug.

51. Wyeth knowingly, intentionally and negligently disseminated misleading information to physicians' across the country, through a publication known as the *Physicians' Desk Reference*, labeling information for Reglan, metoclopramide and metoclopramide HCl which mislead the medical community, physicians and Plaintiff's physician about the increased risk of extrapyramidal side effects, including tardive dyskinesia, diabetics, including Plaintiff, were exposed to.

52. Wyeth manufactured, marketed and distributed Reglan, metoclopramide, and/or metoclopramide HCl through its Wyeth-Ayerst Laboratories Division in St. Davids, Pennsylvania.

53. At all times relevant herein, Wyeth manufactured, marketed and distributed *generic* (also known as "branded generic") Reglan, metoclopramide, and/or metoclopramide HCl through its ownership of ESI LEDERLE, INC. (hereinafter "ESI").[2]

54. Wyeth manufactures and distributes Reglan, branded generic and/or generic metoclopramide and/or metoclopramide HCl through its ownership of ESI Lederle.

55. Defendant Schwarz purchased from Wyeth the rights and *liabilities* associated with Reglan, metoclopramide and metoclopramide HCl tablets, upon information and belief, the terms of which obligated Schwarz to be responsible for claims related to the ingestion or use of Reglan, metoclopramide and metoclopramide HCl, subject to a right of indemnification from Wyeth up to a certain dollar amount.[3]

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[2] Upon information and belief, ESI was a former subsidiary which merged into Wyeth on or about December 15, 1998.

[3] Plaintiff does not have information regarding the maximum amount of liability under the defendants' indemnification agreement.

56. Defendant Schwarz was/and remains the RLD and/or NDA holder, for Reglan, metoclopramide and metoclopramide HCl tablets.

57. Wyeth reviewed the article published in the *Archives of Internal Medicine*, in 1989, and written by Joseph Jankovic, entitled "Metoclopramide-Induced Movement Disorders: A Review of the Literature."

58. Wyeth reviewed the article published in the *Annals of Pharmacology*, in 1992, written by Dr. Ronald Stewart, entitled "An Analysis of Inappropriate Long-Term Use in the Elderly."

59. Wyeth reviewed the epidemiological study published in the medical literature, specifically the *Archives of Internal Medicine*, in June of 1993, and written by Linda Ganzini.

60. Wyeth reviewed the epidemiological study published and written by Dr. Daniel Sewell in 1994, regarding the frequency of tardive dyskinesia in metoclopramide treated patients.

61. Wyeth reviewed the medical literature written by authors, Yassa & Jeste, in 1992, regarding the prevalence of tardive dyskinesia in patients exposed to long term neuroleptic drugs.

62. Schwarz reviewed the article published in the *Archives of Internal Medicine*, in 1989, and written by Joseph Jankovic, entitled "Metoclopramide-Induced Movement Disorders: A Review of the Literature."

63. Schwarz reviewed the article published in the *Annals of Pharmacology*, in 1992, written by Dr. Ronald Stewart, entitled "An Analysis of Inappropriate Long-Term Use in the Elderly."

64. Schwarz reviewed the epidemiological study published in the medical literature, specifically the *Archives of Internal Medicine*, in June of 1993, and written by Linda Ganzini.

65. Schwarz reviewed the epidemiological study published and written by Dr. Daniel Sewell in 1994, regarding the frequency of tardive dyskinesia in metoclopramide treated patients.

66. Schwarz reviewed the medical literature written by authors, Yassa & Jeste, in 1992, regarding the prevalence of tardive dyskinesia in patients exposed to long term neuroleptic drugs.

67. Schwarz had a duty to ensure its warnings to the medical community are accurate and adequate; had a duty to conduct safety surveillance of adverse events for the drug, and to report *any* data related to the safety and/or accuracy of the warnings and information disseminated regarding the drug.

68. Schwarz manufactured, marketed and distributed Reglan, metoclopramide and/or metoclopramide HCl at all relevant material times herein.

69. Wyeth breached its duty to the medical community, Plaintiff's physicians, Plaintiff and

other foreseeable users similarly situated, in that it failed to ensure Reglan, metoclopramide and metoclopramide HCl warnings to the medical community, physicians, Plaintiff's physician and Plaintiff were accurate and adequate.

70. Wyeth breached its joint duty to the medical community, to Plaintiff's physicians, Plaintiff, and other foreseeable users similarly situated, in that it failed to conduct post market safety surveillance and report that information the medical community, Plaintiff's physician, Plaintiff and other like foreseeable users.

71. Wyeth breached its duty to the medical community, Plaintiff's physician, Plaintiff, and other foreseeable users similarly situated, because it failed to review all adverse drug event information (ADE),[4] and to report any information bearing upon the adequacy and/or accuracy of its warnings, efficacy, or safety, including the risks and/or prevalence of side effects caused by Reglan, metoclopramide or metoclopramide HCl, to the medical community, Plaintiff's physician, Plaintiff and other like foreseeable users.

72. Wyeth breached its duty to the medical community, Plaintiff's physician, Plaintiff, and other foreseeable users similarly situated, in that it failed to periodically review all medical literature regarding Reglan, metoclopramide,

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[4] *See* 21 C.F.R. § 317.80(b).

and metoclopramide HCl, and failed to report data, *regardless of the degree of significance*, regarding the adequacy and/or accuracy of its warnings, efficacy, or safety of Reglan, metoclopramide and metoclopramide HCl.

73. Schwarz breached its duty to the medical community, Plaintiff's physician, Plaintiff and other foreseeable users similarly situated, because it failed to ensure Reglan, metoclopramide, and metoclopramide HCl warnings to the medical community were accurate and adequate.

74. Schwarz breached its duty to the medical community, Plaintiff's physician, Plaintiff and other foreseeable users similarly situated, because it failed to conduct post market safety surveillance and failed to report any significant data regarding the adequacy and/or accuracy of its warnings, efficacy, or safety of Reglan, metoclopramide, and/or metoclopramide HCl.

75. Schwarz breached its duty to the medical community, Plaintiff's physician, Plaintiff, and other foreseeable users similarly situated all adverse drug event information (ADE), and to report any information bearing upon the adequacy and/or accuracy of its warnings, efficacy, or safety, including the risks and/or prevalence of side effects caused by Reglan, metoclopramide or metoclopramide HCl, the medical community, Plaintiff's physician, Plaintiff and other like foreseeable users.

76. Schwarz breached its duty to the medical community, Plaintiff's physician, Plaintiff, and other foreseeable users similarly situated because it failed to periodically review all medical literature and failed to report any significant data concerning neurological side effects, *regardless of the degree of significance*, regarding the adequacy and/or accuracy of its warnings, efficacy, or safety of Reglan, metoclopramide, and/or metoclopramide HCl.

77. Defendant PLIVA submitted an Abbreviated New Drug Application to the U.S. Food and Drug Administration, based on representations made by the RLD Company, requesting permission to manufacture, market, and distribute metoclopramide and/or metoclopramide HCl.

78. Under the ANDA process, the Code of Federal Regulations *required* Defendant PLIVA to submit a label for metoclopramide and metoclopramide HCl, initially identical in all material aspects to the reference listed drug label.

79. Defendant PLIVA began selling generic metoclopramide and/or metoclopramide HCl in 1988.

80. PLIVA did not investigate the accuracy of its metoclopramide and/or metoclopramide HCl drug label.

81. PLIVA did not review the medical literature for the metoclopramide drug.

82. PLIVA did not review the medical literature for the metoclopramide and/or metoclopramide HCl drug.

83. PLIVA is under a duty to ensure that its metoclopramide label is accurate.

84. PLIVA did not review the article published in the *Archives of Internal Medicine*, in 1989, and written by Joseph Jankovic, entitled "Metoclopramide-Induced Movement Disorders: A Review of the Literature."

85. PLIVA did not review the article published in the *Annals of Pharmacology*, in 1992, written by Dr. Ronald Stewart, entitled "An Analysis of Inappropriate Long-Term Use in the Elderly."

86. PLIVA did not review the epidemiological study published in the medical literature, specifically the *Archives of Internal Medicine*, in June of 1993, and written by Linda Ganzini.

87. PLIVA did not review the epidemiological study published and written by Dr. Daniel Sewell in 1994, regarding the frequency of tardive dyskinesia in metoclopramide treated patients.

88. PLIVA did not review the medical literature written by authors, Yassa & Jeste, in 1992, regarding the prevalence of tardive dyskinesia in patients exposed to long term neuroleptic drugs.

89. PLIVA relied upon the name brand manufacturer to review the aforementioned medical literature for the metoclopramide drug.

90. PLIVA relied upon the reference listed drug company for the reference listed metoclopramide drug to review the aforementioned medical literature.

91. Under the Code of Federal Regulations, Defendant PLIVA, as an ANDA holder, had a duty to ensure its Reglan, metoclopramide, and metoclopramide HCl warnings to the medical community were accurate and adequate; had a duty to conduct post market safety surveillance; to review all adverse drug event information (ADE), and to report any information bearing on the risk and/or prevalence of side effects caused by Reglan, metoclopramide or metoclopramide HCl, the medical community, Plaintiff's physician, Plaintiff and other foreseeable users.

92. Under the Code of Federal Regulations, if Defendant PLIVA, as the ANDA holder, discovers information in the course of the fulfillment of its duties as outlined above, Defendant PLIVA must report that information to the medical community, Plaintiff's physician, Plaintiff and other foreseeable users of Reglan, metoclopramide and metoclopramide HCl to ensure that its warnings are continually accurate and adequate.

93. PLIVA breached its duty to the medical community, Plaintiff's Physician, Plaintiff, and other foreseeable users similarly situated

because it failed to ensure Reglan, metoclopramide, and/or metoclopramide HCl warnings to the medical community, Plaintiff's physician, Plaintiff, other foreseeable users similarly situated were accurate and adequate.

94. PLIVA breached its duty to the medical community, Plaintiff's physician, Plaintiff, and other foreseeable users similarly situated because it failed to conduct post market safety surveillance of Reglan, metoclopramide, and/or metoclopramide HCl, and failed to report any significant data regarding the adequacy and/or accuracy of its warnings, efficacy, or safety of Reglan, metoclopramide, and/or metoclopramide HCl.

95. PLIVA breached its duty to the medical community, Plaintiff's physician, Plaintiff, and other foreseeable users similarly situated because it failed to review all adverse drug event information (ADE), and to report any information bearing upon the adequacy and/or accuracy of its warnings, efficacy, or safety, including the risks and/or prevalence of side effects caused by Reglan, metoclopramide or metoclopramide HCl, the medical community, Plaintiff's physician, Plaintiff and other like foreseeable users.

96. PLIVA breached its duty to the medical community, Plaintiff's physician, Plaintiff, and other foreseeable users similarly situated because it failed to periodically review all medical literature and failed to report any significant data concerning neurological side

effects, *regardless of the degree of significance*, regarding the adequacy and/or accuracy of its warnings, efficacy, or safety of Reglan, metoclopramide, and/or metoclopramide HCl.

97. PLIVA breached its duty to the medical community, Plaintiff's physician, Plaintiff, and other foreseeable users similarly situated because it failed to communicate the true and accurate risks and/or prevalence of severe neurological side effects resulting from the ingestion of drugs containing the active ingredient metoclopramide and/or metoclopramide HCl.

98. Defendant TEVA submitted an Abbreviated New Drug Application to the U.S. Food and Drug Administration, based on representations made by the RLD Company, requesting permission to manufacture, market, and distribute metoclopramide and/or metoclopramide HCl.

99. Under the ANDA process, the Code of Federal Regulations *required* Defendant Teva to submit a label for metoclopramide and metoclopramide HCl, initially identical in all material aspects as to the reference listed drug label.

100. Teva did not investigate the accuracy of its metoclopramide and/or metoclopramide HCl drug label.

101. Teva did not review the medical literature for the metoclopramide and/or metoclopramide HCl drug.

102. Teva is under a duty to ensure that its metoclopramide label is accurate.

103. Teva did not review the article published in the *Archives of Internal Medicine*, in 1989, and written by Joseph Jankovic, entitled "Metoclopramide-Induced Movement Disorders: A Review of the Literature."

104. Teva did not review the article published in the *Annals of Pharmacology*, in 1992, written by Dr. Ronald Stewart, entitled "An Analysis of Inappropriate Long-Term Use in the Elderly."

105. Teva did not review the epidemiological study published in the medical literature, specifically the *Archives of Internal Medicine*, in June of 1993, and written by Linda Ganzini.

106. Teva did not review the epidemiological study published and written by Dr. Daniel Sewell in 1994, regarding the frequency of tardive dyskinesia in metoclopramide treated patients.

107. Teva did not review the medical literature written by authors, Yassa & Jeste, in 1992, regarding the prevalence of tardive dyskinesia in patients exposed to long term neuroleptic drugs.

108. Teva relied upon the name brand manufacturer to review the aforementioned medical literature for the metoclopramide drug.

109. Teva relied upon the reference listed drug company for the reference listed

metoclopramide drug to review the aforementioned medical literature.

110. Under the Code of Federal Regulations, Defendant Teva, as an ANDA holder, had a duty to ensure its warnings to the medical community were accurate and adequate; had a duty to conduct post market safety surveillance; to review all adverse drug event information (ADE), and to report any information bearing on the risk and/or prevalence of side effects caused by Reglan, metoclopramide or metoclopramide HCl to the medical community, Plaintiff's physician, Plaintiff and other foreseeable users.

111. Under the Code of Federal Regulations, if Defendant Teva, as the ANDA holder, discovers information in the course of the fulfillment of its duties as outlined above, Defendant Teva, must report that information to ensure that its warnings for Reglan, metoclopramide and metoclopramide HCl are continually accurate and adequate.

112. Teva breached its duty to the medical community, Plaintiff's physician, Plaintiff and other foreseeable users similarly situated because it failed to ensure Reglan, metoclopramide, and/or metoclopramide HCl warnings to the medical community, Plaintiff's physician, Plaintiff, other foreseeable users similarly situated were accurate and adequate.

113. Teva breached its duty to the medical community, Plaintiff's physician, Plaintiff, and other foreseeable users similarly situated

because it failed to conduct post market safety surveillance of Reglan, metoclopramide, and/or metoclopramide HCl, and failed to report any significant data regarding the adequacy and/or accuracy of its warnings, efficacy, or safety of Reglan, metoclopramide, and/or metoclopramide HCl.

114. Teva breached its duty to the medical community, the Plaintiff's physician, the Plaintiff, and other foreseeable users similarly situated because it failed to and to report any information bearing upon the adequacy and/or accuracy of its warnings, efficacy, or safety, including the risks and/or prevalence of side effects caused by Reglan, metoclopramide or metoclopramide HCl, the medical community, Plaintiff's physician, Plaintiff and other like foreseeable users.

115. Teva breached its duty to the medical community, the Plaintiff's physician, the Plaintiff, and other foreseeable users similarly situated because it failed to periodically review all medical literature and failed to communicate and report material safety information, as reported in the medical literature, concerning neurological side effects, to the medical community, the Plaintiff's physician, the Plaintiff and other foreseeable users of Reglan/metoclopramide and metoclopramide HCl.

116. Under the ANDA process, the Code of Federal Regulations *required* Defendant UDL Laboratories to submit a label for

metoclopramide and metoclopramide HCl, identical in all material aspects as to the reference listed drug label.

117. Under the Code of Federal Regulations, Defendant UDL Laboratories, as an ANDA holder, has a duty to ensure its warnings to the medical community were accurate and adequate; has a duty to conduct post market safety surveillance; to review all adverse drug event information (ADE), and to report and communicate any information bearing on the risk and/or prevalence of side effects caused by Reglan, metoclopramide or metoclopramide HCl, to the medical community, Plaintiff's physician, Plaintiff and other foreseeable users.

118. Under the Code of Federal Regulations, if Defendant UDL Laboratories, as the ANDA holder, discovers information in the course of the fulfillment of its duties as outlined above, Defendant UDL, must report that information to ensure that its warnings for Reglan, metoclopramide and metoclopramide HCl are continually accurate and adequate.

119. UDL did not investigate the accuracy of its metoclopramide and/or metoclopramide HCl drug label.

120. UDL did not review the medical literature for the metoclopramide drug.

121. UDL did not review the medical literature for the metoclopramide and/or metoclopramide HCl drug.

122. UDL is under a duty to ensure that its metoclopramide label is accurate.

123. UDL did not review the article published in the *Archives of Internal Medicine*, in 1989, and written by Joseph Jankovic, entitled "Metoclopramide-Induced Movement Disorders: A Review of the Literature."

124. UDL did not review the article published in the *Annals of Pharmacology*, in 1992, written by Dr. Ronald Stewart, entitled "An Analysis of Inappropriate Long-Term Use in the Elderly."

125. UDL did not review the epidemiological study published in the medical literature, specifically the *Archives of Internal Medicine*, in June of 1993, and written by Linda Ganzini.

126. UDL did not review the epidemiological study published and written by Dr. Daniel Sewell in 1994, regarding the frequency of tardive dyskinesia in metoclopramide treated patients.

127. UDL did not review the medical literature written by authors, Yassa & Jeste, in 1992, regarding the prevalence of tardive dyskinesia in patients exposed to long term neuroleptic drugs.

128. UDL relied upon the name brand manufacturer to review the aforementioned medical literature for the metoclopramide drug.

129. UDL relied upon the reference listed drug company for the reference listed

metoclopramide drug to review the aforementioned medical literature.

130. UDL Laboratories breached its duty to the medical community, Plaintiff's physician, Plaintiff and other foreseeable users similarly situated because it failed to ensure its warnings regarding Reglan, metoclopramide, and/or metoclopramide HCl to the medical community, Plaintiff's physician, plaintiff and other like foreseeable users, were adequate and accurate.

131. UDL Laboratories breached its duty to the medical community, Plaintiff's physician, Plaintiff, and other foreseeable users similarly situated because it failed to conduct post market safety surveillance of Reglan, metoclopramide, and/or metoclopramide HCl, and failed to report any significant data regarding the adequacy and/or accuracy of its warnings, efficacy, or safety of Reglan, metoclopramide, and/or metoclopramide HCl.

132. UDL Laboratories breached its duty to the medical community, the Plaintiff's physician, the Plaintiff, and other foreseeable users similarly situated and to report any information bearing upon the adequacy and/or accuracy of its warnings, efficacy, or safety, including the risks and/or prevalence of side effects caused by Reglan, metoclopramide or metoclopramide HCl, the medical community, Plaintiff's physician, Plaintiff and other like foreseeable users.

133. UDL Laboratories breached its duty to the medical community, the Plaintiff's physician,

the Plaintiff, and other foreseeable users similarly situated because it failed to periodically review all medical literature and failed to report any significant data concerning neurological side effects, *regardless of the degree of significance*, regarding the adequacy and/or accuracy of its warnings, efficacy, or safety of Reglan, metoclopramide, and/or metoclopramide HCl.

134. Defendant ACTAVIS ELIZABETH, LLC submitted an Abbreviated New Drug Application to the U.S. Food and Drug Administration, based on representations made by the RLD Company, requesting permission to manufacture, market, and distribute metoclopramide and/or metoclopramide HCl.

135. Under the ANDA process, the Code of Federal Regulations *required* Defendant ACTAVIS ELIZABETH, LLC to submit a label for metoclopramide and metoclopramide HCl, identical in all material aspects as to the reference listed drug label.

136. Under the Code of Federal Regulations, Defendant ACTAVIS ELIZABETH, LLC, as an ANDA holder, had a duty to ensure its warnings to the medical community, Plaintiff's physician, Plaintiff and other like foreseeable users were accurate and adequate; had a duty to conduct post market safety surveillance, to review all adverse drug event information (ADE), and to report any information bearing on the risk and/or prevalence of side effects caused by Reglan, metoclopramide or metoclopramide HCl,

to the medical community, Plaintiff's physician, Plaintiff and other foreseeable users.

137. ACTAVIS ELIZABETH, LLC, did not investigate the accuracy of its metoclopramide and/or metoclopramide HCl drug label.

138. ACTAVIS ELIZABETH, LLC, did not review the medical literature for the metoclopramide drug.

139. ACTAVIS ELIZABETH, LLC, did not review the medical literature for the metoclopramide and/or metoclopramide HCl drug.

140. ACTAVIS ELIZABETH, LLC, is under a duty to ensure that its metoclopramide label is accurate.

141. ACTAVIS ELIZABETH, LLC, did not review the article published in the *Archives of Internal Medicine*, in 1989, and written by Joseph Jankovic, entitled "Metoclopramide-Induced Movement Disorders: A Review of the Literature."

142. ACTAVIS ELIZABETH, LLC, did not review the article published in the *Annals of Pharmacology*, in 1992, written by Dr. Ronald Stewart, entitled "An Analysis of Inappropriate Long-Term Use in the Elderly."

143. ACTAVIS ELIZABETH, LLC, did not review the epidemiological study published in the medical literature, specifically the *Archives of Internal Medicine*, in June of 1993, and written by Linda Ganzini.

144. ACTAVIS ELIZABETH, LLC, did not review the epidemiological study published and written by Dr. Daniel Sewell in 1994, regarding the frequency of tardive dyskinesia in metoclopramide treated patients.

145. ACTAVIS ELIZABETH, LLC, did not review the medical literature written by authors, Yassa & Jeste, in 1992, regarding the prevalence of tardive dyskinesia in patients exposed to long term neuroleptic drugs.

146. ACTAVIS ELIZABETH, LLC, relied upon the name brand manufacturer to review the aforementioned medical literature for the metoclopramide drug.

147. ACTAVIS ELIZABETH, LLC, relied upon the reference listed drug company for the reference listed metoclopramide drug to review the aforementioned medical literature.

148. Under the Code of Federal Regulations, if Defendant ACTAVIS ELIZABETH, LLC., as the ANDA holder, discovers information in the course of the fulfillment of its duties as outlined above, Defendant ACTAVIS ELIZABETH, LLC must report that information to ensure that its warnings for Reglan, metoclopramide and metoclopramide HCl are continually accurate and adequate.

149. ACTAVIS ELIZABETH, LLC breached its duty to the medical community, Plaintiff's physician, Plaintiff and other foreseeable users similarly situated because it failed to ensure its warnings

regarding Reglan, metoclopramide, and/or metoclopramide HCl to the medical community, Plaintiff's physician, plaintiff and other like foreseeable users, were adequate and accurate.

150. ACTAVIS ELIZABETH, LLC, breached its duty to the medical community, Plaintiff's physician, Plaintiff, and other foreseeable users similarly situated because it failed to conduct post market safety surveillance of Reglan, metoclopramide, and/or metoclopramide HCl, and failed to report any significant data regarding the adequacy and/or accuracy of its warnings, efficacy, or safety of Reglan, metoclopramide, and/or metoclopramide HCl.

151. ACTAVIS ELIZABETH, LLC breached its duty to the medical community, the Plaintiff's physician, the Plaintiff, and other foreseeable users similarly situated and to report any information bearing upon the adequacy and/or accuracy of its warnings, efficacy, or safety, including the risks and/or prevalence of side effects caused by Reglan, metoclopramide or metoclopramide HCl, to the medical community, Plaintiff's physician, Plaintiff and other like foreseeable users.

152. ACTAVIS ELIZABETH, LLC., breached its duty to the medical community, the Plaintiff's physician, the Plaintiff, and other foreseeable users similarly situated because it failed to periodically review all medical literature and failed to report any significant data concerning neurological side effects, *regardless of the degree of significance*, regarding the adequacy and/or

accuracy of its warnings, efficacy, or safety of Reglan, metoclopramide, and/or metoclopramide HCl.

153. Defendant Purepac submitted an Abbreviated New Drug Application to the U.S. Food and Drug Administration, based on representations made by the RLD Company, requesting permission to manufacture, market, and distribute metoclopramide and/or metoclopramide HCl.

154. Under the ANDA process, the Code of Federal Regulations *required* Defendant Purepac to submit a label for metoclopramide and metoclopramide HCl, identical in all material aspects as to the reference listed drug label.

155. Under the Code of Federal Regulations, Defendant Purepac, as an ANDA holder, had a duty to ensure its warnings to the medical community, Plaintiff's physician, Plaintiff and other like foreseeable users were accurate and adequate; had a duty to conduct post market safety surveillance; to review all adverse drug event information (ADE), and to report any information bearing on the risk and/or prevalence of side effects caused by Reglan, metoclopramide or metoclopramide HCl, to the medical community, Plaintiff's physician, Plaintiff and other foreseeable users.

156. Purepac did not investigate the accuracy of its metoclopramide and/or metoclopramide HCl drug label.

157. Purepac did not review the medical literature for the metoclopramide drug.

158. Purepac did not review the medical literature for the metoclopramide and/or metoclopramide HCl drug.

159. Purepac is under a duty to ensure that its metoclopramide label is accurate.

160. Purepac did not review the article published in the *Archives of Internal Medicine,* in 1989, and written by Joseph Jankovic, entitled "Metoclopramide-Induced Movement Disorders: A Review of the Literature."

161. Purepac did not review the article published in the *Annals of Pharmacology,* in 1992, written by Dr. Ronald Stewart, entitled "An Analysis of Inappropriate Long-Term Use in the Elderly."

162. Purepac did not review the epidemiological study published in the medical literature, specifically the *Archives of Internal Medicine,* in June of 1993, and written by Linda Ganzini.

163. Purepac did not review the epidemiological study published and written by Dr. Daniel Sewell in 1994, regarding the frequency of tardive dyskinesia in metoclopramide treated patients.

164. Purepac did not review the medical literature written by authors, Yassa & Jeste, in 1992, regarding the prevalence of tardive dyskinesia

in patients exposed to long term neuroleptic drugs.

165. Purepac relied upon the name brand manufacturer to review the aforementioned medical literature for the metoclopramide drug.

166. Purepac relied upon the reference listed drug company for the reference listed metoclopramide drug to review the aforementioned medical literature.

167. Under the Code of Federal Regulations, if Defendant Purepac, as the ANDA holder, discovers information in the course of the fulfillment of its duties as outlined above, Defendant Purepac must report that information to ensure that its warnings for Reglan, metoclopramide and metoclopramide HCl are continually accurate and adequate.

168. Purepac breached its duty to the medical community, Plaintiff's physician, Plaintiff and other foreseeable users similarly situated because it failed to ensure its warnings regarding Reglan, metoclopramide, and/or metoclopramide HCl to the medical community, Plaintiff's physician, plaintiff and other like foreseeable users, were adequate and accurate.

169. Purepac breached its duty to the medical community, Plaintiff's physician, Plaintiff, and other foreseeable users similarly situated because it failed to conduct post market safety surveillance of Reglan, metoclopramide, and/or metoclopramide HCl, and failed to report any

significant data regarding the adequacy and/or accuracy of its warnings, efficacy, or safety of Reglan, metoclopramide, and/or metoclopramide HCl.

170. Purepac breached its duty to the medical community, the Plaintiff's physician, the Plaintiff, and other foreseeable users similarly situated and to report any information bearing upon the adequacy and/or accuracy of its warnings, efficacy, or safety, including the risks and/or prevalence of side effects caused by Reglan, metoclopramide or metoclopramide HCl, to the medical community, Plaintiff's physician, Plaintiff and other like foreseeable users.

171. Purepac breached its duty to the medical community, the Plaintiff's physician, the Plaintiff, and other foreseeable users similarly situated because it failed to periodically review all medical literature and failed to report any significant data concerning neurological side effects, *regardless of the degree of significance*, regarding the adequacy and/or accuracy of its warnings, efficacy, or safety of Reglan, metoclopramide, and/or metoclopramide HCl.

172. The generic defendants named herein relied upon the data and information for the reference listed drug at issue in this litigation to evaluate safety and efficacy of their generic metoclopramide and/or metoclopramide HCl drug.

173. The generic defendants label for metoclopramide and/or metoclopramide HCl

utilized the same safety, efficacy and warnings regarding extrapyramidal side effects of this drug.

174. If a generic drug company learns of side effects, risks or misleading and inaccurate information in the Reglan, metoclopramide and metoclopramide HCl label, it must request and/or submit labeling revision for the drug.

175. The generic defendants knew or should have known about the side effects, risks, misleading and inaccurate information contained in the Reglan, metoclopramide and metoclopramide HCl and knowingly and intentionally withheld that information and or failed to report that information to the medical community, physicians, Plaintiff's physicians and other foreseeable users.

176. Under the FDA schema, if the FDA approves a label change as requested by an ANDA holder, the NDA holder (also referred to as the Reference Listed Drug Company) ***must amend*** its label.

177. The NDA holder and each individual ANDA holder are under a joint duty to ensure its warnings to the medical community, Plaintiff's physician, Plaintiff and other foreseeable users are accurate and adequate for their drug products.

178. The NDA holder and all ANDA holders are under a joint duty to ensure that their drugs, specifically Reglan, metoclopramide and

metoclopramide HCl warnings to the medical community, Plaintiff's physician, Plaintiff and foreseeable users alike, are accurate and adequate at all times.

179. Defendant WYETH, by and through ESI Lederle (a/k/a ESI, a/k/a Lederle) submitted an Abbreviated New Drug Application to the U.S. Food and Drug Administration, based on representations made by the RLD Company, requesting permission to manufacture, market, and distribute metoclopramide and/or metoclopramide HCl.

180. Under the ANDA process, the Code of Federal Regulations *required* Defendant WYETH, by and through ESI Lederle (a/k/a ESI, a/k/a Lederle) to submit a label for metoclopramide and metoclopramide HCl drugs based upon data, information and representations materially identical to the reference listed drug label for that drug.

181. Defendant WYETH, by and through ESI Lederle (a/k/a ESI, a/k/a Lederle), as an ANDA holder, had a duty to ensure its warnings to the medical community were accurate and adequate; had a duty to conduct post market safety surveillance; to review all adverse drug experience information (ADE) and to report any data (medical literature) regarding the adequacy and accuracy of the risk and or prevalence of contracting a severe neurological disorder.

182. Under the Code of Federal Regulations, if Defendant WYETH, by and through ESI Lederle

(a/k/a ESI, a/k/a Lederle), as the ANDA holder, discovers information in the course of the fulfillment of its duties as outlined above, Defendant WYETH, by and through ESI Lederle (a/k/a ESI, a/k/a Lederle), must report that information to the medical community, Plaintiff's physician, plaintiff and other foreseeable users.

183. WYETH, by and through ESI Lederle (a/k/a ESI, a/k/a Lederle) breached its duty to the medical community, Plaintiff's physician, Plaintiff and other foreseeable users similarly situated because it failed to ensure its warnings regarding Reglan, metoclopramide, and/or metoclopramide HCl to the medical community, Plaintiff's physician, plaintiff and other like foreseeable users, were adequate and accurate.

184. WYETH, by and through ESI Lederle (a/k/a ESI, a/k/a Lederle), breached its duty to the medical community, Plaintiff's physician, Plaintiff, and other foreseeable users similarly situated because it failed to conduct post market safety surveillance of Reglan, metoclopramide, and/or metoclopramide HCl, and failed to report any significant data regarding the adequacy and/or accuracy of its warnings, efficacy, or safety of Reglan, metoclopramide, and/or metoclopramide HCl.

185. WYETH, by and through ESI Lederle (a/k/a ESI, a/k/a Lederle) breached its duty to the medical community, the Plaintiff's physician, the Plaintiff, and other foreseeable users similarly situated because it failed to report any

information bearing upon the adequacy and/or accuracy of its warnings, efficacy, or safety, including the risks and/or prevalence of side effects caused by Reglan, metoclopramide or metoclopramide HCl, the medical community, Plaintiff's physician, Plaintiff and other like foreseeable users.

186. WYETH, by and through ESI Lederle (a/k/a ESI, a/k/a Lederle), breached its duty to the medical community, the Plaintiff's physician, the Plaintiff, and other foreseeable users similarly situated because it failed to periodically review all medical literature and failed to report any significant data concerning neurological side effects, *regardless of the degree of significance*, regarding the adequacy and/or accuracy of its warnings, efficacy, or safety of Reglan, metoclopramide, and/or metoclopramide HCl.

187. Federal regulations impose a joint duty on the NDA holder and all ANDA holders to conduct post market safety surveillance and to communicate any significant data regarding the adequacy and/or accuracy of its warnings, efficacy, or safety of Reglan, metoclopramide and metoclopramide HCl to the medical community, Plaintiff's physician,Plaintiff, and other foreseeable users of Reglan/ metoclopramide and metoclopramide HCl.

188. The NDA holder and all ANDA holders are under a joint duty to review all adverse drug

experience information (ADE)[5] and to report any significant date regarding the adequacy and/or accuracy of its warnings, efficacy, or safety of Reglan, metoclopramide and metoclopramide HCl to the medical community, physicians, Plaintiff's physician, plaintiff and other foreseeable users.

189. The NDA holder and ANDA holders are under a joint duty to periodically review all medical literature and to report any significant data, no matter the degree of significance, regarding the adequacy and/or accuracy of its warnings, efficacy, or safety of Reglan, metoclopramide and metoclopramide HCl to ensure that its labels are continually accurate and adequate.

190. Wyeth and Schwarz, NDA holders and Teva, ANDA holder, jointly breached their duty to the medical community, including Plaintiff's physician, Plaintiff and other foreseeable users alike, in that they failed to ensure Reglan, metoclopramide and metoclopramide HCl warnings to the medical community, including Plaintiff's physician and/or Plaintiff, were accurate and adequate.

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[5] Defendants are required to review all adverse drug experience information

> obtained or otherwise received...from any source...including derived from postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports from the scientific literature, and unpublished scientific reports

21 C.F.R. § 317.80(b).

191. Wyeth and Schwarz, NDA holders and Defendant Teva, ANDA holder, jointly breached their joint duty to the medical community, including Plaintiff's physicians, Plaintiff, and other foreseeable users alike because they failed to conduct post market safety surveillance of Reglan, metoclopramide, and/or metoclopramide HCl, and failed to report any significant data regarding the adequacy and/or accuracy of its warnings, efficacy, or safety of Reglan, metoclopramide, and/or metoclopramide.

192. Wyeth and Schwarz, NDA holders and Teva, ANDA holder, jointly breached their duty to the medical community, including Plaintiff's physicians and Plaintiff because they failed to report any information bearing upon the adequacy and/or accuracy of its warnings, efficacy, or safety, including the risks and/or prevalence of side effects caused by Reglan, metoclopramide or metoclopramide HCl, to the medical community, Plaintiff's physician, Plaintiff and other like foreseeable users.

193. Wyeth and Schwarz, NDA holders and Teva, ANDA holder, jointly breached their duty to the medical community, including Plaintiff's physicians and Plaintiff in that it failed to periodically review all medical literature and failed to report any significant data concerning neurological side effects, *regardless of the degree of significance*, regarding the adequacy and/or accuracy of its warnings, efficacy, or safety of Reglan, metoclopramide, and/or metoclopramide HCl.

194. Wyeth and Schwarz, NDA holders and PLIVA, ANDA holder, jointly breached their duty to the medical community, including Plaintiff's physician, Plaintiff and other foreseeable users alike, in that they failed to ensure Reglan, metoclopramide and metoclopramide HCl warnings to the medical community, including Plaintiff's physician and/or Plaintiff, were accurate and adequate.

195. Wyeth and Schwarz, NDA holders and Defendant PLIVA, ANDA holder, jointly breached their joint duty to the medical community, including Plaintiff's physicians, Plaintiff, and other foreseeable users alike because they failed to conduct post market safety surveillance of Reglan, metoclopramide, and/or metoclopramide HCl, and failed to report any significant data regarding the adequacy and/or accuracy of its warnings, efficacy, or safety of Reglan, metoclopramide, and/or metoclopramide HCl.

196. Wyeth and Schwarz, NDA holders and PLIVA, ANDA holder, jointly breached their duty to the medical community, including Plaintiff's physicians and Plaintiff because it failed to review adverse drug experience information (hereinafter "ADE") and to report any significant data gleaned from that review regarding the adequacy and/or accuracy of its warnings, efficacy, or safety of Reglan, metoclopramide and metoclopramide HCl.

197. Wyeth and Schwarz, NDA holders and PLIVA, ANDA holder, jointly breached their duty to the

medical community, including Plaintiff's physicians and Plaintiff in that they failed to periodically review all medical literature and failed to report any significant data concerning neurological side effects, *regardless of the degree of significance*, regarding the adequacy and/or accuracy of its warnings, efficacy, or safety of Reglan, metoclopramide, and/or metoclopramide HCl.

198. Wyeth and Schwarz, NDA holders and UDL Laboratories, ANDA holder, jointly breached their duty to the medical community, including Plaintiff's physician, Plaintiff and other foreseeable users alike, in that they failed to ensure Reglan, metoclopramide and metoclopramide HCl warnings to the medical community, including Plaintiff's physician and/or Plaintiff, were accurate and adequate.

199. Wyeth and Schwarz, NDA holders and Defendant UDL Laboratories, ANDA holder, jointly breached their joint duty to the medical community, including Plaintiff's physicians, Plaintiff, and other foreseeable users alike because they failed to conduct post market safety surveillance of Reglan, metoclopramide, and/or metoclopramide HCl, and failed to report any significant data regarding the adequacy and/or accuracy of its warnings, efficacy, or safety of Reglan, metoclopramide, and/or metoclopramide HCl.

200. Wyeth and Schwarz, NDA holders and UDL Laboratories, ANDA holder, jointly breached their duty to the medical community, including

Plaintiff's physicians and Plaintiff because they failed to communicate material safety information bearing upon the adequacy and/or accuracy of its warnings, efficacy, or safety, including the risks and/or prevalence of side effects caused by Reglan, metoclopramide or metoclopramide HCl, to the medical community, Plaintiff's physician, Plaintiff and other like foreseeable users.

201. Wyeth and Schwarz, NDA holders and UDL Laboratories, ANDA holder, jointly breached their duty to the medical community, including Plaintiff's physicians and Plaintiff in that it failed to periodically review all medical literature and failed to report any significant data concerning neurological side effects, *regardless of the degree of significance,* regarding the adequacy and/or accuracy of its warnings, efficacy, or safety of Reglan, metoclopramide, and/or metoclopramide HCl.

202. Wyeth and Schwarz, NDA holders and UDL Laboratories, ANDA holder, jointly breached their duty to the medical community, including Plaintiff's physician, Plaintiff and other foreseeable users alike, in that they failed to ensure Reglan, metoclopramide and metoclopramide HCl warnings to the medical community, including Plaintiff's physician and/or Plaintiff, were accurate and adequate.

203. Wyeth and Schwarz, NDA holders and Defendant UDL Laboratories, ANDA holder, jointly breached their joint duty to the medical community, including Plaintiff's physicians,

Plaintiff , and other foreseeable users alike because they failed to conduct post market safety surveillance of Reglan, metoclopramide, and/or metoclopramide HCl, and failed to report any significant data regarding the adequacy and/or accuracy of its warnings, efficacy, or safety of Reglan, metoclopramide, and/or metoclopramide HCl.

204. Wyeth and Schwarz, NDA holders and UDL Laboratories, ANDA holder, jointly breached their duty to the medical community, including Plaintiff's physicians and Plaintiff because it failed to review adverse drug experience information (hereinafter "ADE") and to report any significant data gleaned from that review regarding the adequacy and/or accuracy of its warnings, efficacy, or safety of Reglan, metoclopramide and metoclopramide HCl to the medical community, Plaintiff's physician, Plaintiff and other foreseeable uses of Reglan/metoclopramide and metoclopramide HCl.

205. Wyeth and Schwarz, NDA holders and UDL Laboratories, ANDA holder, jointly breached their duty to the medical community, including Plaintiff's physicians and Plaintiff in that it failed to periodically review all medical literature and failed to communicate any significant data concerning neurological side effects, regarding the adequacy and/or accuracy of its warnings, efficacy, or safety of Reglan, metoclopramide, and/or metoclopramide HCl to the medical community, Plaintiff's physician,

Plaintiff and other foreseeable users of Reglan, metoclopramide and metoclopramide HCl.

206. Wyeth and Schwarz, NDA holders and WYETH, by and through ESI Lederle (a/k/a ESI, a/k/a Lederle), ANDA holder, jointly breached their duty to the medical community, including Plaintiff's physician, Plaintiff and other foreseeable users alike, in that they failed to ensure Reglan, metoclopramide and metoclopramide HCl warnings to the medical community, including Plaintiff's physician and/or Plaintiff, were accurate and adequate.

207. Wyeth and Schwarz, NDA holders and Defendant WYETH, by and through ESI Lederle (a/k/a ESI, a/k/a Lederle), ANDA holder, jointly breached their joint duty to the medical community, including Plaintiff's physicians, Plaintiff, and other foreseeable users alike because they failed to conduct post market safety surveillance of Reglan, metoclopramide, and/or metoclopramide HCl, and failed to report any significant data regarding the adequacy and/or accuracy of its warnings, efficacy, or safety of Reglan, metoclopramide, and/or metoclopramide HCl.

208. Wyeth and Schwarz, NDA holders and WYETH, by and through ESI Lederle (a/k/a ESI, a/k/a Lederle), ANDA holder, jointly breached their duty to the medical community, including Plaintiff's physicians and Plaintiff because it failed to review and to report any information bearing upon the adequacy and/or accuracy of its warnings, efficacy, or safety, including the

risks and/or prevalence of side effects caused by Reglan, metoclopramide or metoclopramide HCl, the medical community, Plaintiff's physician, Plaintiff and other like foreseeable users.

209. Wyeth and Schwarz, NDA holders and WYETH, by and through ESI Lederle (a/k/a ESI, a/k/a Lederle), ANDA holder, jointly breached their duty to the medical community, including Plaintiff's physicians and Plaintiff in that it failed to periodically review all medical literature and failed to report any significant data concerning neurological side effects, *regardless of the degree of significance,* regarding the adequacy and/or accuracy of its warnings, efficacy, or safety of Reglan, metoclopramide, and/or metoclopramide HCl.

210. Wyeth and Schwarz, NDA holders and ACTAVIS ELIZABETH, LLC , ANDA holder, jointly breached their duty to the medical community, including Plaintiff's physician, Plaintiff and other foreseeable users alike, in that they failed to ensure Reglan, metoclopramide and metoclopramide HCl warnings to the medical community, including Plaintiff's physician and/or Plaintiff, were accurate and adequate.

211. Wyeth and Schwarz, NDA holders and Defendant ACTAVIS ELIZABETH, LLC , ANDA holder, jointly breached their joint duty to the medical community, including Plaintiff's physicians, Plaintiff, and other foreseeable users alike because they failed to conduct post market safety surveillance of Reglan,

metoclopramide, and/or metoclopramide HCl, and failed to report any significant data regarding the adequacy and/or accuracy of its warnings, efficacy, or safety of Reglan, metoclopramide, and/or metoclopramide.

212. Wyeth and Schwarz, NDA holders and ACTAVIS ELIZABETH, LLC, ANDA holder, jointly breached their duty to the medical community, including medical community, including Plaintiff's physician, Plaintiff and other foreseeable users alike because it and to report any information bearing upon the adequacy and/or accuracy of its warnings, efficacy, or safety, including the risks and/or prevalence of side effects caused by Reglan, metoclopramide or metoclopramide HCl, the medical community, Plaintiff's physician, Plaintiff and other like foreseeable users.

213. Wyeth and Schwarz, NDA holders and ACTAVIS ELIZABETH, LLC, ANDA holder, jointly breached their duty to the medical community, Plaintiff's physician, Plaintiff and other foreseeable users of Reglan/ metoclopramide and metoclopramide HCl in that they failed to periodically review all medical literature and failed to communicate material safety data and information concerning neurological side effects, of this drug which effected the adequacy and/or accuracy of its warnings, efficacy, or safety of Reglan, metoclopramide, and/or metoclopramide HCl to the medical community, Plaintiff's physician, Plaintiff and other foreseeable users of Reglan, metoclopramide and metoclopramide HCl.

214. ACTAVIS ELIZABETH, LLC, UDL Laboratories, WYETH, by and through ESI Lederle (a/k/a ESI, a/k/a Lederle), Teva, Pliva, Wyeth, and Schwarz jointly and severally, marketed, manufactured and distributed Reglan, metoclopramide and/or metoclopramide HCl and encouraged the long term use of these drugs, misrepresented the effectiveness of these drugs and concealed the drug's dangerous side effects.

215. The drugs Reglan, metoclopramide and/or metoclopramide HCl were widely advertised by the Drug Company Defendants as a safe and effective treatment of diabetic gastroparesis, gastroesophageal reflux disease (GERD) and other gastrointestinal disorders.

216. At all times material hereto, Defendant Wyeth, individually and as successor-in-interest to A.H. Robins Company, as the NDA holder and RLD company, was aware of the serious side effects caused by Reglan/metoclopramide including, but not limited to, central nervous system disorders, depression with suicidal ideation, akathesia, tardive dyskinesia, tardive dystonia, visual disturbances and interference with drug metabolism and failed to fulfill its obligation to report and divulge said side effects, and in doing so, mislead the medical community, physicians, plaintiff's physician, plaintiff and other foreseeable users about the safety of the long term use of the drug.

217. At all times material hereto, Defendant Schwarz, as the NDA holder and RLD company,

respectively, was aware of the serious side effects caused by Reglan/metoclopramide including, but not limited to, central nervous system disorders, depression with suicidal ideation, akathesia, tardive dyskinesia, tardive dystonia, visual disturbances and interference with drug metabolism.

218. At all times material hereto, Defendant Wyeth, individually and as successor-in-interest to A.H. Robins Company, as the NDA holder and RLD company, knew or should have known that physicians were **not** aware of or did not fully appreciate the seriousness of the risks associated with use of Reglan/metoclopramide and that consequently there was a widespread tendency for physicians to prescribe Reglan/metoclopramide for long-term use.

219. At all times material hereto, Defendant Schwarz, as the NDA holder/RLD Company and purchaser of the innovator's Reglan, metoclopramide and metoclopramide HCl interest, knew or should have known that physicians were **not** aware of or did not fully appreciate the seriousness of the risks associated with use of Reglan/metoclopramide and that consequently there was a widespread tendency for physicians to prescribe Reglan/metoclopramide for long-term use.

220. The DRUG COMPANY DEFENDANTS knew or should have known that the package insert and the Physician Desk Reference monograph for Reglan/metoclopramide did not adequately inform physicians about the risks associated

with Reglan/metoclopramide, particularly for patients whose bodies do not metabolize Reglan, metoclopramide, and/or metoclopramide HCl effectively, yet said Defendants failed to communicate said information to the medical community, Plaintiff's physicians, Plaintiff or other foreseeable users alike, and in doing so, mislead the medical community, physicians, plaintiff's physician, plaintiff and other foreseeable users about the safety of the long term use of this drug.

221. Schwarz as the NDA holder and/or Referenced Listed Drug holder(s), failed to report safety information regarding severe side effects of Reglan, metoclopramide, and metoclopramide HCl, it knew or should have known from a review of information it was privy to by virtue of its indemnification agreement with Wyeth, from a review of data from clinical studies that were not publicly available, through its review of domestic and international medical literature concerning Reglan/ metoclopramide and through ongoing litigation involving Reglan, metoclopramide and metoclopramide HCl and in doing so, mislead the medical community, physicians, plaintiff's physician, plaintiff and other foreseeable users about the safety of the long term use of the drug.

222. Defendant Wyeth knew, or should have known through the exercise of reasonable care, that the package insert for Reglan/metoclopramide substantially understated the prevalence of acute and long term side effects of Reglan/metoclopramide.

223. Wyeth failed to use reasonable care to modify the package insert to adequately warn physicians about the true risks of both short term use and long term use, even after several injured patients filed lawsuits alleging inadequate warnings and produced competent expert testimony supporting their allegations.

224. Defendant Schwarz knew or should have known through the exercise of reasonable care, that the package insert for Reglan/metoclopramide substantially understated the prevalence of acute and long term side effects of Reglan/metoclopramide.

225. Schwarz failed to use reasonable care to modify the package insert to adequately warn physicians about the true risks of both short term use and long term use, even after several injured patients filed lawsuits alleging inadequate warnings and produced competent expert testimony supporting their allegations.

226. Defendant PLIVA, as an ANDA holder, knew, or should have known through the exercise of reasonable care, that the package insert for Reglan/metoclopramide substantially understated the prevalence of acute and long term side effects of Reglan/metoclopramide.

227. PLIVA failed to use reasonable care to modify the package insert to adequately warn physicians about the true risks of both short term use and long term use, even after several injured patients filed lawsuits alleging

inadequate warnings and produced competent expert testimony supporting their allegations.

228. Defendant Teva, as an ANDA holder, knew, or should have known through the exercise of reasonable care, that the package insert for Reglan/metoclopramide substantially understated the prevalence of acute and long term side effects of Reglan/metoclopramide.

229. Teva failed to use reasonable care to modify the package insert to adequately warn physicians about the true risks of both short term use and long term use, even after several injured patients filed lawsuits alleging inadequate warnings and produced competent expert testimony supporting their allegations.

230. Defendant UDL Laboratories, as an ANDA holder, knew, or should have known through the exercise of reasonable care, that the package insert for Reglan/metoclopramide substantially understated the prevalence of acute and long term side effects of Reglan/metoclopramide.

231. UDL Laboratories failed to use reasonable care to modify the package insert to adequately warn physicians about the true risks of both short term use and long term use, even after several injured patients filed lawsuits alleging inadequate warnings and produced competent expert testimony supporting their allegations.

232. Defendant ACTAVIS ELIZABETH, LLC, as an ANDA holder, knew, or should have known through the exercise of reasonable care, that the

package insert for Reglan/metoclopramide substantially understated the prevalence of acute and long term side effects of Reglan/metoclopramide.

233. ACTAVIS ELIZABETH, LLC failed to use reasonable care to modify the package insert to adequately warn physicians about the true risks of both short term use and long term use, even after several injured patients filed lawsuits alleging inadequate warnings and produced competent expert testimony supporting their allegations.

234. Defendant WYETH, by and through ESI Lederle (a/k/a ESI, a/k/a Lederle), as an ANDA holder, knew, or should have known through the exercise of reasonable care, that the package insert for Reglan/metoclopramide substantially understated the prevalence of acute and long term side effects of Reglan/metoclopramide.

235. WYETH, by and through ESI Lederle (a/k/a ESI, a/k/a Lederle) failed to use reasonable care to modify the package insert to adequately warn physicians about the true risks of both short term use and long term use, even after several injured patients filed lawsuits alleging inadequate warnings and produced competent expert testimony supporting their allegations.

236. Defendant PUREPAC, as an ANDA holder, knew, or should have known through the exercise of reasonable care, that the package insert for Reglan/metoclopramide substantially

understated the prevalence of acute and long term side effects of Reglan/metoclopramide.

237. Purepac failed to use reasonable care to modify the package insert to adequately warn physicians about the true risks of both short term use and long term use, even after several injured patients filed lawsuits alleging inadequate warnings and produced competent expert testimony supporting their allegations.

238. Defendants failed and continue to fail to use reasonable care to modify the package insert for Reglan, metoclopramide and metoclopramide HCl, to adequately and accurately warn the medical community, Plaintiff's physician, and plaintiff about the true risks of both short term use and long term use, even after numerous injured patients filed lawsuits alleging inadequate warnings and produced competent expert testimony supporting their allegations.

239. Defendant Wyeth and its predecessors in interest had actual knowledge, through their own studies and studies by independent investigators, that doctors frequently prescribed Reglan/metoclopramide for long term use that was not safe for patients.

240. Defendants Schwarz and its predecessors in interest had actual knowledge, through their own studies and studies by independent investigators, that doctors frequently prescribed Reglan/metoclopramide for long term use that was not safe for patients.

241. Defendant Wyeth and its predecessors in interest had actual knowledge, through their own studies and studies by independent investigators, that nearly one-third of all patients who used Reglan/metoclopramide received it on doctor's prescriptions for 12 months or longer, rather than 12 weeks or less.

242. Defendant Wyeth also had actual knowledge, through research by independent investigators, that the risk of tardive dyskinesia and other extrapyramidal side effects of Reglan/metoclopramide in patients who receive the drug for 12 weeks or longer is approximately 100 times greater than disclosed in Wyeth's package insert for Reglan and the Physicians Desk Reference monograph for Reglan brand metoclopramide and failed to correct their monograph and/or disclose that knowledge to the medical community, physicians, plaintiff's physician, plaintiff and other foreseeable users.

243. Defendant Wyeth knew, or through the exercise of reasonable care should have known, that many patients who use Reglan/metoclopramide are not able to effectively metabolize Reglan/metoclopramide and that as a foreseeable consequence of their inability to effectively metabolize Reglan/metoclopramide, those patients have a greater risk of developing serious and permanent injuries, which it failed to disclose this material safety information to the medical community and failed to adequately disclose to the generic pharmaceutical industry.

244. Defendant Wyeth willfully and in wanton disregard of the rights of Plaintiff and other persons in Plaintiff's class, failed to disclose and communicate material safety information regarding the risks of this drug to the medical community, Plaintiff's physician, Plaintiff and other like foreseeable users, knowing that such failure would result in serious injury to patients who were prescribed Reglan/metoclopramide by a physician who was not aware of this information.

245. Defendant Wyeth knew, or through the exercise of reasonable care should have known, that many patients who use Reglan/metoclopramide are not able to effectively metabolize Reglan/metoclopramide and that as a foreseeable consequence of their inability to effectively metabolize Reglan/metoclopramide, those patients have a greater risk of developing serious and permanent injuries, but failed to communicate this material safety information to the medical community, Plaintiff's physician, Plaintiff and other like foreseeable users, knowing that such failure would result in serious injury to patients who were prescribed Reglan/metoclopramide by a physician who was not aware of this information.

246. Defendant Schwarz in interest had actual knowledge, through their own studies and studies by independent investigators, that nearly one-third of all patients who used Reglan/metoclopramide received it on doctor's prescriptions for 12 months or longer, rather than 12 weeks or less.

247. Defendant Schwarz also had actual knowledge, through research by independent investigators, that the risk of tardive dyskinesia and other extrapyramidal side effects of Reglan/ metoclopramide in patients who receive the drug for 12 weeks or longer is approximately 100 times greater than disclosed in Wyeth's package insert for Reglan and the Physicians Desk Reference monograph for Reglan brand metoclopramide and failed to correct their monograph and/or disclose that knowledge to the medical community, physicians, plaintiff's physician, plaintiff and other foreseeable users.

248. Defendant Schwarz knew, or through the exercise of reasonable care should have known, that many patients who use Reglan/ metoclopramide are not able to effectively metabolize Reglan/metoclopramide and that as a foreseeable consequence of their inability to effectively metabolize Reglan/metoclopramide, those patients have a greater risk of developing serious and permanent injuries, but it failed to communicate this material safety information regarding the risks to the medical community, Plaintiff's physician, Plaintiff and other like foreseeable users, knowing that such failure would result in serious injury to patients who were prescribed Reglan/metoclopramide by a physician who was not aware of this information.

249. Defendant Schwarz willfully and in wanton disregard of the rights of Plaintiff and other persons in Plaintiff's class, failed to communicate the aforesaid information to the

medical community, Plaintiff's physician, Plaintiff and other like foreseeable users, knowing that such failure would result in serious injury to patients who were prescribed Reglan/metoclopramide by a physician who was not aware of this information.

250. Defendant Schwarz knew, or through the exercise of reasonable care should have known, that many patients who use Reglan/metoclopramide are not able to effectively metabolize Reglan/metoclopramide and that as a foreseeable consequence of their inability to effectively metabolize Reglan/metoclopramide, those patients have a greater risk of developing serious and permanent injuries, but failed to communicate this material safety information to the medical community, Plaintiff's physician, Plaintiff and other like foreseeable users, knowing that such failure would result in serious injury to patients who were prescribed Reglan/metoclopramide by a physician who was not aware of this information.

251. Defendant Schwarz willfully and in wanton disregard of the rights of Plaintiff and other persons in Plaintiff's class, failed to communicate the material safety information to the medical community, Plaintiff's physician, Plaintiff and other like foreseeable users, knowing that such failure would result in serious injury to patients who were prescribed Reglan/metoclopramide by a physician who was not aware of this information.

252. Defendant Schwarz failed to disclose *any* information regarding the adequacy and accuracy of the warnings for Reglan, metoclopramide and metoclopramide HCl and/or safety or efficacy of the drug with the full knowledge that such failure, would result in serious injury to patients who were prescribed Reglan/metoclopramide by a physician who was not aware of this information, and thereby acted in willful and wanton disregard of the rights of persons in the Plaintiff's class, and this conduct caused serious injury to the Plaintiff.

253. Wyeth misrepresented the safety of Reglan, metoclopramide and metoclopramide HCl, and withheld warnings of the known side effects the drug as commonly prescribed by physicians.[6]

254. Defendant Wyeth, individually and as successor-in-interest to A.H. Robins Company, was aware of the serious side effects caused by Reglan/metoclopramide including, but not limited to, central nervous system disorders, depression with suicidal ideation, akathesia, tardive dyskinesia, tardive dystonia, visual disturbances and interference with drug metabolism, yet breached its duty to the medical community, Plaintiff's physician, Plaintiff and other like foreseeable users by failing to communicate such side effects, to the medical community, Plaintiff's physician, Plaintiff and other foreseeable users.

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[6] *See* 21 C.F.R. § 201.128.

255. Wyeth breached its duty, as the NDA holder and/or Referenced Listed Drug Company for Reglan, metoclopramide and metoclopramide HCl, by misrepresenting the safety and efficacy of the drug, with the intent to defraud and deceive physicians, including Plaintiff's physician, and through them to defraud and deceive Plaintiff, with the intent to induce practitioners to use Reglan/metoclopramide as pharmaceutical treatment for diabetic gastroparesis for a period of time that far exceeded the FDA's approved indicated duration of use.

256. Wyeth as an NDA holder and/or Referenced Listed Drug Company for Reglan, metoclopramide and metoclopramide HCl, knew or should have known that a patient was at a significantly increased risk of developing a severe and permanent neurological movement disorder from the long term ingestion of Reglan, metoclopramide and metoclopramide HCl, given the published medical literature.

257. As set forth above, Wyeth as an NDA holder and/or Referenced Listed Drug Company for Reglan, metoclopramide and metoclopramide HCl, and its predecessors falsely and fraudulently represented to physicians, Plaintiff's physicians, and to foreseeable users, including Plaintiff, that the drug was safe to use in the treatment of diabetic gastropaeries and that permanent neurological side effects were comparatively rare.

258. As set forth above, Wyeth as an NDA holder and/or Referenced Listed Drug Company for Reglan, metoclopramide and metoclopramide HCl, and its predecessors falsely and fraudulently failed to disclose to the medical community, physicians, plaintiff's physician, plaintiff and other foreseeable users that the long term use of the drug at issue, exposed diabetics, including Plaintiff, to a greater risk of extrapyramidal side effects than the non-diabetic user.

259. All Drug Company defendants negligently and intentionally failed to disclose to the medical community, physician, plaintiff's physician, plaintiff and other foreseeable users that patients with diabetes who were exposed to metoclopramide were more likely to develop tardive dyskinesia than metoclopramide-treated non-diabetics.

260. Wyeth as an NDA holder and/or Referenced Listed Drug Company for Reglan, metoclopramide and metoclopramide HCl and its predecessors did not disclose or warn physicians about the actual prevalence of known side effects of Reglan/metoclopramide, particularly when Reglan/metoclopramide is used on a ***long term basis***, as marketed by Wyeth, or when used in patients who are poor metabolizers of metoclopramide, all of which were foreseeable.

261. At the time Wyeth as an NDA holder and/or Referenced Listed Drug Company for Reglan, metoclopramide and metoclopramide HCl and

its predecessors made the above described representations, Plaintiff and Plaintiff's physicians were ignorant of the falsity of the representations and reasonably believed them to be true.

262. Schwarz breached its duty as the NDA holder and/or Referenced Listed Drug Company for Reglan, metoclopramide and metoclopramide HCl, by misrepresenting the safety and efficacy of the drug, with the intent to defraud and deceive physicians, including Plaintiff's physician, and through them to defraud and deceive Plaintiff, with the intent to induce practitioners to use Reglan/metoclopramide as pharmaceutical treatment for diabetic gastropaeries for a period of time that far exceeded the FDA's approved indicated duration of use.

263. Schwarz as an NDA holder and/or Referenced Listed Drug Company for Reglan, metoclopramide and metoclopramide HCl, knew or should have known that a patient was at a significantly increased risk of developing a severe and permanent neurological movement disorder from the long term ingestion of Reglan, metoclopramide and metoclopramide HCl, given the published medical literature.

264. As set forth above, Schwarz as an NDA holder and/or Referenced Listed Drug Company for Reglan, metoclopramide and metoclopramide HCl, and its predecessors falsely and fraudulently represented to physicians, Plaintiff's physicians, and to foreseeable users,

including Plaintiff, that the drug was safe to use in the treatment of diabetic gastropaeries and that permanent neurological side effects were comparatively rare. These representations were, in fact, false. The true facts were that Reglan/metoclopramide was not safe for that purpose and was, in fact, dangerous to the health and body of Plaintiff.

265. Schwarz as an NDA holder and/or Referenced Listed Drug Company for Reglan, metoclopramide and metoclopramide HCl and its predecessors did not disclose or warn physicians about the actual prevalence of known side effects of Reglan/metoclopramide, particularly when Reglan/metoclopramide is used on a ***long term basis***, as marketed by Schwarz, or when used in patients who are poor metabolizers of metoclopramide, all of which were foreseeable.

266. At the time Schwarz, as an NDA holder and/or Referenced Listed Drug Company for Reglan, metoclopramide and metoclopramide HCl and its predecessors made the above described representations, Plaintiff and Plaintiff's physicians were ignorant of the falsity of the representations and reasonably believed them to be true.

267. In reliance upon the representations of Schwarz and Wyeth as the NDA holder and/or Referenced Listed Drug Company for Reglan, metoclopramide and metoclopramide HCl and its predecessors Plaintiff's physicians were

induced to and did prescribe Plaintiff Reglan, metoclopramide and/or metoclopramide HCl.

268. If Plaintiff's' physicians had known the actual risk posed to Plaintiff, particularly the increased risk posed to Plaintiff, as a diabetics, he/she would not have prescribed Reglan to Plaintiff.

269. Plaintiff justifiably relied on Plaintiff's physicians, and Plaintiff reasonably relied upon the representations of Wyeth and Schwarz, as the NDA holder and/or Referenced Listed Drug Company/ innovator of Reglan.

270. Plaintiff's physicians reasonably believed as prudent physicians would that Defendants Wyeth and Schwarz would fully, truthfully and accurately disclose the risks of side effects associated with Reglan, metoclopramide and/or metoclopramide HCl in their drug label, *Physicians Desk Reference* and other literature and data.

271. Plaintiff's serious and permanent injuries, as described above, came about as a foreseeable and proximate result of Wyeth's breach of its duty as an NDA holder and/or Referenced Listed Drug Company for Reglan, metoclopramide and metoclopramide HCl and its predecessors, dissemination to physicians of inaccurate, misleading, materially incomplete, false and otherwise inadequate information concerning the potential side effects of Reglan, metoclopramide and/or metoclopramide HCl.

272. Plaintiff's serious and permanent injuries, as described above, came about as a foreseeable and proximate result of Schwarz's breach of its duty as an NDA holder and/or Referenced Listed Drug Company for Reglan, metoclopramide and metoclopramide HCl, dissemination to physicians of inaccurate, misleading, materially incomplete, false and otherwise inadequate information concerning the potential side effects of Reglan, metoclopramide and/or metoclopramide HCl.

273. In doing the acts alleged in this Complaint, Wyeth and its predecessors acted with oppression, fraud, and malice and Plaintiff is therefore entitled to punitive damages to deter Wyeth and others from engaging in similar conduct in the future.

274. Wyeth's wrongful conduct was done with the advance knowledge, authorization, or ratification of an officer, director, or managing agent of each of Wyeth and its predecessors.

275. In doing the acts alleged in this Complaint, Schwarz acted with oppression, fraud, and malice and Plaintiff is therefore entitled to punitive damages to deter Schwarz and others from engaging in similar conduct in the future.

276. Schwarz's wrongful conduct was done with the advance knowledge, authorization, or ratification of an officer, director, or managing agent of each of Schwarz and its predecessors.

277. As a proximate result of the fraud and deceit of Wyeth and its predecessors, Plaintiff sustained the injuries and damages as described in this Complaint.

278. As a proximate result of the fraud and deceit of Schwarz, Plaintiff sustained the injuries and damages as described in this Complaint.

279. Defendant Schwarz breached its duty as the NDA holder and/or Referenced Listed Drug Company for Reglan, metoclopramide and metoclopramide HCl, because it misrepresented the safety of Reglan, metoclopramide and metoclopramide HCl, and withheld warnings of the known side effects of the drug as commonly prescribed by physicians when it knew or should have known of the safety issues surrounding Reglan, metoclopramide and metoclopramide HCl.

280. Because Defendant Schwarz acquired Defendant Wyeth's Reglan, metoclopramide and metoclopramide HCl, assets and liabilities, while Wyeth was involved in ongoing litigation regarding Reglan, metoclopramide and metoclopramide HCl, and nevertheless agreed to indemnify Wyeth against all claims related to the ingestion of Reglan, metoclopramide and metoclopramide HCl, Schwarz knew or should have known that the NDA label for Reglan, metoclopramide and metoclopramide HCl (Wyeth's label) misrepresented the safety of Reglan, metoclopramide and metoclopramide HCl; withheld warnings of the known side effects of the drug; and knew or should have

known of the safety issues surrounding Reglan, metoclopramide and metoclopramide HCl.

281. Defendant Schwarz breached its duty to the medical community, Plaintiff's physician, Plaintiff and other like foreseeable users, because it intentionally and fraudulently made statements to defraud and deceive the medical community, Plaintiff, and other foreseeable users of this drug, and Plaintiff's physician, with the intent to induce practitioners to use Reglan/metoclopramide as pharmaceutical treatment for diabetic gastropaeries for a period of time that far exceeded the FDA's approved indicated duration of use.

282. As set forth above, Schwarz as an NDA holder and/or Referenced Listed Drug Company for Reglan, metoclopramide and metoclopramide HCl, and its predecessors falsely and fraudulently represented to physicians, Plaintiff's physicians, and to foreseeable users, including Plaintiff, that the drug was safe to use in the treatment of diabetic gastropaeries and that permanent neurological side effects were comparatively rare. These representations were, in fact, false. The true facts were that Reglan/metoclopramide was not safe for that purpose and was, in fact, dangerous to the health and body of Plaintiff.

283. Schwarz as an NDA holder and/or Referenced Listed Drug Company for Reglan, metoclopramide and metoclopramide HCl and its predecessors did not disclose or warn physicians about the actual prevalence of known

side effects of Reglan/metoclopramide, particularly when Reglan/metoclopramide is used on a ***long term basis***, as marketed by Wyeth *and/or* Schwarz, or when used in patients who are poor metabolizers of metoclopramide, all of which were foreseeable.

284. Schwarz did not disclose or warn physicians about the true risks and prevalence of known side extrapyramidal side effects of Reglan/ metoclopramide, particularly when Reglan/ metoclopramide is used on a ***long term basis***, by diabetics, all of which were foreseeable.

285. At the time Schwarz as an NDA holder and/or Referenced Listed Drug Company for Reglan, metoclopramide and metoclopramide HCl and its predecessors made the above described representations, Plaintiff and Plaintiff's physicians were ignorant of the falsity of the representations and reasonably believed them to be true.

286. In reliance upon the representations of Schwarz as the NDA holder and/or Referenced Listed Drug Company for Reglan, metoclopramide and metoclopramide HCl and its predecessors Plaintiff's physicians were induced to and did prescribe Plaintiff Reglan, metoclopramide and/or metoclopramide HCl.

287. Plaintiff's serious and permanent injuries, as described above, came about as a foreseeable and proximate result of Schwarz's breach of its duty as an NDA holder and/or Referenced Listed Drug Company of Reglan, metoclopramide and

metoclopramide HCl, and manufacturer, in failing to correct false and misleading information it disseminated to physicians, which contained inaccurate, misleading, materially incomplete, false and otherwise inadequate information concerning the efficacy, safety and potential side effects of Reglan, metoclopramide and/or metoclopramide HCl.

288. In doing the acts alleged in this Complaint, Schwarz acted with oppression, fraud, and malice and Plaintiff is therefore entitled to punitive damages to deter Schwarz and others from engaging in similar conduct in the future.

289. As a proximate result of the fraud and deceit of Schwarz and its predecessors in interest, Plaintiff sustained the injuries and damages as described in this Complaint.

290. Wyeth and Schwarz had actual knowledge of facts which demonstrated that representations in the Reglan, metoclopramide and metoclopramide HCl package insert, PDR monograph and literature that they distributed concerning Reglan, metoclopramide and metoclopramide HCl to physicians was false and misleading.

291. Wyeth had an absolute duty to disclose the true facts regarding the safety of Reglan, metoclopramide and metoclopramide HCl to the medical community, to physicians and their patients, pharmacists, and the generic metoclopramide industry, which they negligently and/or intentionally failed to do.

292. Schwarz had an absolute duty to disclose the true facts regarding the safety of Reglan, metoclopramide and metoclopramide HCl to the medical community, to physicians and their patients, pharmacists, and the generic metoclopramide industry, which it negligently and/or intentionally failed to do.

293. Wyeth had a duty to ensure that it had a reasonable basis for making the representations regarding the safety, efficacy, risks and benefits of Reglan, metoclopramide and metoclopramide HCl, were accurate and was under at duty to exercise reasonable care in making those representations, to accurately make those representations, and to not make misrepresentations, all of which it negligently and/or intentionally failed to do.

294. Schwarz had a duty to ensure that it had a reasonable basis for making the representations regarding the safety, efficacy, risks and benefits of Reglan, metoclopramide and metoclopramide HCl, were accurate and was under at duty to exercise reasonable care in making those representations, to accurately make those representations, and to not make misrepresentations, all of which it negligently and/or intentionally failed to do.

295. Wyeth and Schwarz failed to report important information and data relating to Reglan, metoclopramide and metoclopramide HCl risks, side effects and prevalence of extrapyramidal side effects, which information was in the exclusive control of Wyeth and Schwarz and was

exclusively known by them, and thus breached their duty to the medical community, Plaintiff's Physician, Plaintiff and other like foreseeable users, and thereby putting Plaintiff and other like foreseeable users at harm.

296. To further its own profits and interests, Wyeth disseminated false and misleading information regarding the safety and efficacy of Reglan, metoclopramide and metoclopramide HCl to the medical community, Plaintiff's physician, pharmacists, Plaintiff and other like foreseeable users, and did so knowing that the safety of metoclopramide users depended on the accuracy of that information.

297. To further its own profits and interests, Schwarz disseminated false and misleading information regarding the safety and efficacy of Reglan, metoclopramide and metoclopramide HCl to the medical community, Plaintiff's physician, pharmacists, Plaintiff and other like foreseeable users, and did so knowing that the safety of metoclopramide users depended on the accuracy of that information.

298. Wyeth knew and expected the medical community, physicians, pharmacists, Plaintiff's physician, Plaintiff and other like foreseeable users of Reglan, metoclopramide and metoclopramide HCl, would rely on the information Wyeth disseminated, that said individuals would take action based upon that information, and that Plaintiff and other like foreseeable users who ingested said drug would be put in peril by Wyeth's dissemination of false

and misleading information and would suffer physical harm as a result.

299. Schwarz knew and expected the medical community, physicians, pharmacists, Plaintiff's physician, Plaintiff and other like foreseeable users of Reglan, metoclopramide and metoclopramide HCL, would rely on the information Schwarz disseminated, that said individuals would take action based upon that information, and that Plaintiff and other like foreseeable users who ingested said drug would be put in peril by Schwarz's dissemination of false and misleading information and would suffer physical harm as a result.

300. Wyeth expressly and/or impliedly represented to the medical community, physicians, pharmacists, Plaintiff's physician, Plaintiff and other like foreseeable users that Reglan/ metoclopramide was safe for long term use and that the risk of developing a severe neurological movement disorder was "rare" when in fact long term use *significantly* increases a patient's risk of contracting said disorder.

301. Schwarz expressly and/or impliedly represented to the medical community, physicians, pharmacists, Plaintiff's physician, Plaintiff and other like foreseeable users that Reglan/ metoclopramide was safe for long term use and that the risk of developing a severe neurological movement disorder was "rare" when in fact long term use *significantly* increases a patient's risk of contracting said disorder.

302. Wyeth and Schwarz falsely misrepresented that Reglan, metoclopramide and metoclopramide HCl was safe for long term use even though it *did not* conduct any studies regarding long term use; failed to present accurate or sufficient information concerning these truth of these representations; and failed to exercise reasonable care in disseminating accurate and truthful information regarding long term use.

303. Wyeth's misrepresentations or omissions were made to the medical community, physicians across the nation, Plaintiff's physician, Plaintiff, Plaintiff's pharmacists, the generic pharmaceutical industry and foreseeable users of the drug, all of whom justifiably and foreseeably relied on those representations or omissions.

304. Schwarz's misrepresentations or omissions were made to the medical community, physicians across the nation, Plaintiff's physician, Plaintiff, Plaintiff's pharmacists, the generic pharmaceutical industry and foreseeable users of the drug, all of whom justifiably and foreseeably relied on those representations or omissions.

305. Plaintiff would not have suffered Plaintiff's injuries but for the above misrepresentations or omissions of Wyeth.

306. Plaintiff would not have suffered Plaintiff's injuries but for the above misrepresentations or omissions of Schwarz.

307. Wyeth's misrepresentations or omissions were a cause in fact and a proximate cause of Plaintiff's damages.

308. Schwarz's misrepresentations or omissions were a cause in fact and a proximate cause of Plaintiff's damages.

309. At all times mentioned in this Complaint, Wyeth and its predecessors had the duty and obligation to disclose to the medical community, Physicians, Plaintiff's physicians, Plaintiff and other like foreseeable users, the true facts concerning true level of risk involved in prescribing Reglan/metoclopramide for the purposes indicated.

310. Wyeth and its predecessors made the affirmative representations set forth above to Plaintiff, Plaintiff's prescribing physicians, and the general public prior to the day Plaintiff was first prescribed and used Reglan/ metoclopramide while concealing the material facts regarding the safety and efficacy of said drug.

311. At all times mentioned in this Complaint, Schwarz had the duty and obligation to disclose to the medical community, Physicians, Plaintiff's physicians, Plaintiff and other like foreseeable users, the true facts concerning true level of risk involved in prescribing Reglan, metoclopramide and metoclopramide HCl associated with long term use.

312. Schwarz made the affirmative representations set forth above to the medical community, physicians, Plaintiff, Plaintiff's physicians, and other foreseeable users, prior to the day Plaintiff was first prescribed and used Reglan/ metoclopramide while concealing the material facts regarding the safety and efficacy of said drug.

313. Wyeth and its predecessors had the duty and obligation, to disclose to the medical community, Physicians, Plaintiff's physician, Plaintiff and other like foreseeable users, the true facts concerning Reglan/ metoclopramide that is that long term use and exposure could cause central nervous system side effects, including but not limited to, akathesia, akinesia, tardive dyskinesia and tardive dystonia.

314. Schwarz and its predecessors had the duty and obligation, to disclose to the medical community, Physicians, Plaintiff's physician, Plaintiff and other like foreseeable users, the true facts concerning Reglan/ metoclopramide that long term use and exposure could cause central nervous system side effects, including but not limited to, akathesia, akinesia, tardive dyskinesia and tardive dystonia.

315. Wyeth and its predecessors intentionally, willfully and maliciously concealed or suppressed the risks and prevalence of extrapyramidal side effects associated with the long term use of this drug, from the medical community, physicians, Plaintiff's physicians, and therefore from Plaintiff, and other like

foreseeable users, with the intent to defraud as alleged in this Complaint.

316. Plaintiff nor Plaintiff's physicians were aware of the facts set forth above. Had they been aware of those facts, they would not have acted as they did, that is, would not have utilized Reglan, metoclopramide and metoclopramide HCl in the treatment of Plaintiff's diabetic gastroparesis for periods of time that exceeded 12 weeks duration.

317. As a proximate result of the concealment or suppression of the facts set forth above, Plaintiff was prescribed and took Reglan/metoclopramide and subsequently contracted a severe permanent neurological disorder, thereby sustaining the injuries and damages as set forth in this Complaint.

318. In doing the acts alleged in this Complaint, Wyeth and its predecessors acted with oppression, fraud, and malice, and Plaintiff is therefore entitled to punitive damages in an amount reasonably related to Plaintiff's actual damages and to Wyeth's wealth, and sufficiently large to be an example to others and to deter Wyeth and others from engaging in similar conduct in the future.

319. At all times mentioned in this Complaint, the DRUG COMPANY DEFENDANTS had a duty to properly manufacture, compound, test, inspect, package, label, distribute, market, examine, maintain, supply, provide proper

warnings, and prepare for use and sell Reglan, metoclopramide and metoclopramide HCl.

320. At all times mentioned in this Complaint, the DRUG COMPANY DEFENDANTS had a duty to truthfully, accurately and fully disclose information and data which would reflect that the risks of extrapyramidal side effects clearly outweighed the utility of the Reglan, metoclopramide, and/or metoclopramide HCl or its therapeutic benefits to patients, specifically, elderly female diabetic patients.

321. At all times mentioned in this Complaint, the DRUG COMPANY DEFENDANTS manufactured, compounded, tested, inspected, packaged, labeled, distributed, marketed, examined, maintained, supplied, provided warnings, and prepared for use and sold Reglan, metoclopramide and metoclopramide HCl.

322. The DRUG COMPANY DEFENDANTS knew or should have known that use of metoclopramide created an unreasonable risk as a result of its design, testing, and/or manufacturing, including an unreasonable risk of central nervous system side effects, including but not limited to, depression, akathesia, akinesia, tardive dyskinesia, tardive dystonia, visual disturbances and/or interference with drug metabolism.

323. The DRUG COMPANY DEFENDANTS knew or should have known that use of metoclopramide created an unreasonable risk as a result of its design, testing, and/or manufacturing, including

an unreasonable risk of central nervous system side effects, including but not limited to, depression, akathesia, akinesia, tardive dyskinesia, tardive dystonia, visual disturbances and/or interference with drug metabolism in elderly female diabetic patients.

324. The DRUG COMPANY DEFENDANTS were negligent, and breached their duties owed to the medical community, Physicians, Plaintiff's physician, Plaintiff and other like foreseeable users, with respect to Reglan, metoclopramide and metoclopramide HCl in one or more of the following respects:

(a) Despite knowledge of hazards and knowledge that the Reglan, metoclopramide, and metoclopramide HCl was frequently prescribed for long term use, they failed to accompany the Reglan, metoclopramide, and/or metoclopramide HCl with adequate warnings and instructions regarding the adverse and long lasting side effects associated with the use of metoclopramide and particularly with foreseeable long term use;

(b) They failed to conduct adequate testing;

(c) Despite knowledge of hazards, they failed to conduct adequate post-marketing surveillance to determine the safety of the Reglan, metoclopramide, and/or metoclopramide HCl;

(d) Despite knowledge of hazards, they failed to adequately warn Plaintiff's physicians or Plaintiff that the use of metoclopramide could result in serious side effects, including but not limited to depression with suicidal ideation, akathesia, akinesia, tardive dyskinesia, tardive dystonia, visual disturbances and interferences with drug metabolism, and

(e) Despite the fact that the Drug Company Defendants knew or should have known that metoclopramide caused unreasonably dangerous side effects, they failed to adequately disclose the known or knowable risks associated with Reglan, metoclopramide and metoclopramide HCl and willfully and deliberately failed to adequately disclose these risks, and in doing so, acted with a conscious disregard of Plaintiff's safety or welfare and the safety and welfare of other foreseeable users of Reglan, metoclopramide and metoclopramide HCl.

(f) Despite the fact that the Drug Company Defendants knew or should have known that metoclopramide caused unreasonably an increased risk of extrapyramidal side effects to elderly female diabetic patients, they failed to adequately disclose the known or knowable risks associated with Reglan, metoclopramide and metoclopramide HCl and willfully and deliberately failed to adequately disclose these risks, and in

doing so, acted with a conscious disregard of Plaintiff's safety or welfare and the safety and welfare of other like foreseeable users of Reglan, metoclopramide and metoclopramide HCl.

325. As a result of the negligence of the DRUG COMPANY DEFENDANTS and their willful and wanton misconduct, Reglan, metoclopramide and/or metoclopramide HCl was prescribed to Plaintiff for long term use and was used as prescribed, thereby causing Plaintiff to sustain reasonably foreseeable serious and permanent damages and injuries as alleged in this complaint.

326. The negligence and the willful and wanton misconduct of the DRUG COMPANY DEFENDANTS was a proximate cause of Plaintiff's harm and injuries that Plaintiff has suffered and will continue to suffer.

327. At all times mentioned in this Complaint, metoclopramide was defective and/or unreasonably dangerous to Plaintiff and other foreseeable users at the time it left the control of the DRUG COMPANY DEFENDANTS.

328. Reglan, metoclopramide and metoclopramide HCl was "defective" and "unreasonably dangerous" when the drug was promoted and entered into the stream of commerce and was received by Plaintiff, in one or more of the following respects:

(a) At the time metoclopramide left the control of the DRUG COMPANY DEFENDANTS it was defective and unreasonably dangerous due to a failure to contain adequate warnings or instructions, or, in the alternative, because it was designed in a defective manner, or, in the alternative, because the Reglan, metoclopramide, and/or metoclopramide HCl breached an express warranty or failed to conform to other expressed factual representations upon which Plaintiff's physicians justifiably relied, or because it breached an implied warranty, all of which proximately caused the damages for which Plaintiff seeks recovery herein.

(b) Metoclopramide was not reasonably safe as designed, taking into account the foreseeable risks involved in its use at the time the Reglan, metoclopramide, and/or metoclopramide HCl left the possession of the DRUG COMPANY DEFENDANTS, and that such risks clearly outweighed the utility of the Reglan, metoclopramide, and/or metoclopramide HCl or its therapeutic benefits.

(c) At the time metoclopramide left the control of the DRUG COMPANY DEFENDANTS it possessed a dangerous characteristic that may cause damage and it was not reasonably safe due to inadequate or defective warnings or

instructions that were known or reasonably scientifically knowable at the time the Reglan, metoclopramide, and/or metoclopramide HCl left the possession of the DRUG COMPANY DEFENDANTS. Specifically, although the DRUG COMPANY DEFENDANTS were well aware that metoclopramide could potentially cause central nervous system side effects, including but not limited to, depression with suicidal ideation, akathesia, akinesia, tardive dyskinesia, tardive dystonia, visual disturbances and interference with the metabolism of other prescription drugs and in fact, had significantly greater prevalence and severity of these side effects in patients with diabetes mellitus, warnings of such adverse health conditions were either not included on the package insert for these Reglan, metoclopramide, and/or metoclopramide HCl or they were not adequate to inform reasonably prudent physicians and foreseeable users. The DRUG COMPANY DEFENDANTS failed to use reasonable care to provide an adequate warning of these dangerous characteristics to handlers and users of metoclopramide.

(d) The DRUG COMPANY DEFENDANTS' warnings or instructions were not of a nature that a reasonably prudent drug company in the same or similar circumstances would have provided with respect to the danger. There were no

warnings or instructions that communicate sufficient information on the dangers and safe use of the Reglan, metoclopramide, and/or metoclopramide HCl taking into account the characteristics of the Reglan, metoclopramide, and/or metoclopramide HCl, and/or the ordinary knowledge common to the physician who prescribes and the consumer who purchases the Reglan, metoclopramide, and/or metoclopramide HCl, such as the Plaintiff.

(e) The metoclopramide manufactured and supplied by the DRUG COMPANY DEFENDANTS was further defective due to inadequate post-marketing warning or instruction because, after the DRUG COMPANY DEFENDANTS knew or should have known of the risks of injury from Metoclopramide associated with long term use as commonly prescribed, they failed to promptly respond to and adequately warn about extrapyramidal side effects to foreseeable users.

(f) The metoclopramide manufactured and supplied by the DRUG COMPANY DEFENDANTS was further defective due to inadequate post-marketing warning or instruction because, after the DRUG COMPANY DEFENDANTS knew or should have known of the risks of injury from Reglan/metoclopramide and/or metoclopramide HCl associated with long

term use as commonly prescribed, they failed to promptly respond to and adequately warn about an increased risk as reported in the medical literature for elderly patients for permanent neuological movement disorders, particularly the risk associated with the long term use of Reglan, metoclopramide, and/or metoclopramide HCl posed to diabetic patients, who were foreseeable users of the drug.

329. The DRUG COMPANY DEFENDANTS, individually and collectively, knew, or in light of reasonably available scientific knowledge should have known, about the danger that caused the injuries for which Plaintiff seeks recovery.

330. A reasonably competent physician who prescribed metoclopramide and a reasonably competent Plaintiff who consumed metoclopramide would not realize its dangerous condition.

331. The DRUG COMPANY DEFENDANTS, individually and collectively, knew or in light of reasonably available scientific knowledge should have known about the danger associated with use of metoclopramide that caused the damages for which Plaintiff seeks recovery.

332. The reasonably foreseeable use of metoclopramide, that is ingestion as treatment for diabetic gastroparesis on a long term basis, involved substantial dangers not readily recognizable by Plaintiff's physician, who acted

as an ordinary reasonable and prudent physicians would, when prescribing metoclopramide to an ordinary, reasonable and prudent patient, like Plaintiff.

333. The DRUG COMPANY DEFENDANTS knew that the Reglan, metoclopramide and metoclopramide HCl which was to be prescribed by physicians and used by foreseeable users without inspection for defects in the Reglan, metoclopramide, and/or metoclopramide HCl or in any of its components or ingredients and that metoclopramide was not properly prepared nor accompanied by adequate warnings of its dangerous propensities that were known or reasonably scientifically knowable at the time of distribution.

334. Plaintiff and Plaintiff's physicians did not know, nor had reason to know, at the time of the use of metoclopramide, or at any time prior to its use, of the existence of the above-described defects and inadequate warnings.

335. These defects caused serious injuries to Plaintiff when the Reglan, metoclopramide, and/or metoclopramide HCl was used in its intended and foreseeable manner, and in the manner recommended by the DRUG COMPANY DEFENDANTS or in a non-intended manner that was reasonably foreseeable.

336. Defendant Wyeth's predecessor in interest, A.H. Robins Company, Inc. expressly warranted to some physicians that Reglan/metoclopramide is safe in long-term use.

337. A.H. Robins knew that is its warranties regarding safety for long term use, would be relied upon by ordinary, reasonable and prudent physicians who would share that information with other physicians in their community and that eventually physicians would come to rely on A.H. Robins' express warranties about Reglan/metoclopramide's safety in long-term use.

338. A.H. Robins' express warranties about the safety of Reglan/metoclopramide in long-term use were false and intentionally and/or negligently misleading.

339. As successor in interest to A.H. Robins Company, Inc., Wyeth is legally responsible for the conduct, fraudulent and negligent acts and/or intentional and willful omissions and/or misleading representations and warranties made by A.H. Robins Company, Inc., concerning the safety and adequacy of Reglan/metoclopramide, and liable for injuries which may result therefrom.

340. PLIVA is legally responsible for the conduct, fraudulent and negligent acts and/or intentional and willful omissions and/or misleading representations and warranties made by PLIVA and/or parent corporation, Pliva d.d., concerning the safety and adequacy of Reglan/metoclopramide and/or metoclopramide HCl and liable for injuries which may result therefrom.

341. As successor in interest to Purepac, Defendant Alpharma, is legally responsible for the conduct, fraudulent and negligent acts and/or intentional and willful omissions and/or misleading representations and warranties made by, concerning the safety and adequacy of Reglan/metoclopramide, and liable for injuries which may result therefrom.

342. The DRUG COMPANY DEFENDANTS knew that most physicians who prescribed metoclopramide were not aware the drug is a dopamine antagonist and/or a neuroleptic agent, which is just as likely to cause serious extrapyramidal side effects as other dopamine antagonists and/or other neuroleptic drugs.

343. The DRUG COMPANY DEFENDANTS also knew that the risks of potentially irreversible neurological side effects when metoclopramide is used long term were much greater than most physicians realized. By failing to give adequate warnings about the dopamine antagonist and/or neuroleptic properties of metoclopramide and the risk of long term use that is associated with those properties, the DRUG COMPANY DEFENDANTS breached implied warranties of merchantability and fitness for the ordinary use of metoclopramide.

344. At all times mentioned in this Complaint, the DRUG COMPANY DEFENDANTS manufactured, compounded, packaged, distributed, recommended, merchandised, advertised, promoted, supplied and sold metoclopramide and prior to the time it was

used by Plaintiff, the DRUG COMPANY DEFENDANTS impliedly warranted to Plaintiff and to Plaintiff's physicians that the Reglan, metoclopramide, and/or metoclopramide HCl was of merchantable quality and safe and fit for the use for which it was intended.

345. Plaintiff relied on the skill and judgment of the DRUG COMPANY DEFENDANTS in using metoclopramide as prescribed.

346. Metoclopramide was unsafe and unfit for its intended use, nor was it of merchantable quality, as warranted by the DRUG COMPANY DEFENDANTS, in that it had very dangerous propensities when put to its intended use and would cause severe injury to the user. Metoclopramide was not properly prepared nor accompanied by adequate warnings of its dangerous propensities that were either known or reasonably scientifically knowable at the time of distribution. As a result, the drug proximately caused Plaintiff to sustain damages and injuries as alleged in this Complaint by virtue of causing Plaintiff's illness.

347. By virtue of their individual and collective acts and omissions, Defendants are jointly and severally liable to Plaintiff as such acts and omissions have proximately caused Plaintiff to suffer a single indivisible injury for which each Defendant is responsible.

348. Plaintiff is entitled to recovery an award for the injuries caused by the DRUG COMPANY Defendants.

349. As a direct and proximate result of the aforesaid acts of and/or omissions by the DRUG COMPANY Defendants, individually and jointly, Plaintiff, has:

(a) suffered severe and permanent injuries, which she will be forced to endure for the remainder of Plaintiff's life;

(b) suffered physical impairment and disfigurement;

(c) suffered physical pain and suffering;

(d) suffered mental pain and suffering;

(e) had Plaintiff's enjoyment of life severely impaired; incurred and will continue to incur various sums of money for past, present and future medical expenses associated with monitoring and treating Plaintiff's injuries; and incurred attorney's fees and expenses of litigation related to this action.

350. DRUG COMPANY Defendants actions were intentional, willful, wanton, oppressive, malicious, and reckless, evidencing such an entire want of care as to raise the presumption of a conscious indifference to the consequences and acted only out of self interest and personal gain and evidenced a specific intent to cause harm to Plaintiff.

V. WRONGFUL CONDUCT

COUNT 1

STRICT PRODUCTS LIABILITY

351. Plaintiff repeats, reiterates, and realleges each and every allegation contained in this Complaint with the same force and effect as if fully set forth herein.

352. At all relevant times the DRUG COMPANY DEFENDANTS were engaged in the business of manufacturing, designing, testing, marketing, promoting, distributing, and/or selling metoclopramide.

353. Drug Company defendants, developed, marketed and distributed Reglan, metoclopramide and/or metoclopramide HCl to the general public even after learning of the design and manufacturing defects that threatened the intended use of the drug.

354. Reglan, metoclopramide and/or metoclopramide HCl was defective and unreasonably dangerous and was expected to and did reach Plaintiff without substantial change in the drug.

355. At all times mentioned in this Complaint, metoclopramide was defective and/or unreasonably dangerous to Plaintiff and other foreseeable users at the time it left the control of the DRUG COMPANY DEFENDANTS.

356. Drug company defendants knew or should have known through testing, adverse event reporting, or otherwise, that the drug created a high risk of bodily injury and serious harm.

357. The dangerous propensities of Reglan, metoclopramide and/or metoclopramide HCl products, were known or scientifically knowable, through appropriate research and testing, to the DRUG COMPANY DEFENDANTS at the time said Defendants distributed, supplied, or sold the products, and not known to ordinary physicians who would be expected to prescribe the drug for their patients, or their patients.

358. The Reglan, metoclopramide and/or metoclopramide HCl products, as distributed by the DRUG COMPANY DEFENDANTS, were defective and unreasonably dangerous inasmuch as they were not accompanied by warnings and instructions that were appropriate and adequate to render the products reasonably safe for their ordinary, intended, and reasonably foreseeable uses, in particular the common, foreseeable, and intended use of the products for long term Reglan, metoclopramide and/or metoclopramide HCl therapy.

359. Prior to the manufacturing, sale and distribution of said drug products, DRUG COMPANY DEFENDANTS, and each of them, knew that said drug products were in a defective condition as previously described, and knew that said drug products were in a defective condition as previously described, and knew that those who were prescribed and took

the same would experience, and did experience, severe physical, mental and emotional injuries.

360. DRUG COMPANY DEFENDANTS, and each of them, through their officers, directors and managing agents, had prior notice and knowledge from several sources, prior to the date of dispensing of said drug products to Plaintiff, that the drugs presented a substantial and unreasonable risk of harm to the public, including Plaintiff, and as such said consumers of said drugs were unreasonably subjected to risk of injury or death from the consumption of said drugs.

361. Despite such knowledge, DRUG COMPANY DEFENDANTS, and each of them, acting through their officers, directors and managing agents, for the purpose of enhancing DRUG COMPANY DEFENDANTS' profits, knowingly and deliberately failed to warn the public, including Plaintiff, of the extreme risk of physical injury occasioned by said defects inherent in said drugs. DRUG COMPANY DEFENDANTS intentionally proceeded with the manufacturing, the sale and distribution, and marketing of the drugs with knowledge that consumers would be exposed to serious danger in order to advance DRUG COMPANY DEFENDANTS own pecuniary interest.

362. The Reglan, metoclopramide and/or metoclopramide HCl products, as distributed by the DRUG COMPANY DEFENDANTS, were defective and unreasonably dangerous inasmuch as they were not accompanied by warnings and

instructions that were appropriate and adequate to render the products reasonably safe for their ordinary, intended, and reasonably foreseeable uses, in particular the common, foreseeable, and intended use of the products for long term Reglan, metoclopramide and/or metoclopramide HCl therapy.

363. As a proximate result, Plaintiff suffered grievous bodily injuries and consequent economic and other losses when Plaintiff ingested, as prescribed, Reglan, metoclopramide and/or metoclopramide HCl, which had been developed, manufactured, labeled, marketed, distributed, promoted and/or sold, either directly or indirectly, by DRUG COMPANY DEFENDANTS through third parties or related entities.

364. Reglan/metoclopramide was "defective" and "unreasonably dangerous" when the product initially was patented, and subsequently when it was promoted and entered into the stream of commerce and was received by Plaintiff, in one or more of the following respects:

(a) At the time metoclopramide left the control of the DRUG COMPANY DEFENDANTS it was defective and unreasonably dangerous due to a failure to contain adequate warnings or instructions, or, in the alternative, because it was designed in a defective manner, or, in the alternative, because the product breached an express warranty or failed to conform to other

expressed factual representations upon which Plaintiff's physicians justifiably relied, or because it breached an implied warranty, all of which proximately caused the damages for which Plaintiff seeks recovery herein.

(b) Metoclopramide was not reasonably safe as designed, taking into account the foreseeable risks involved in its use at the time the product left the possession of the DRUG COMPANY DEFENDANTS, and that such risks clearly outweighed the utility of the product or its therapeutic benefits.

(c) At the time metoclopramide left the control of the DRUG COMPANY DEFENDANTS it possessed a dangerous characteristic that may cause damage and it was not reasonably safe due to inadequate or defective warnings or instructions that were known or reasonably scientifically knowable at the time the product left the possession of the DRUG COMPANY DEFENDANTS. Specifically, although the DRUG COMPANY DEFENDANTS were well aware that metoclopramide could potentially cause central nervous system side effects, depression with suicidal ideation, akathesia, akinesia, tardive dyskinesia, tardive dystonia, visual disturbances and interference with the metabolism of other prescription drugs and in fact, had significantly greater

prevalence and severity of these side effects in patients with diabetes mellitus, warnings of such adverse health conditions were either not included on the package insert for these products or they were not adequate to inform reasonably prudent physicians and consumers. The DRUG COMPANY DEFENDANTS failed to use reasonable care to provide an adequate warning of these dangerous characteristics to handlers and users of metoclopramide.

(d) The DRUG COMPANY DEFENDANTS' warnings or instructions were not of a nature that a reasonably prudent drug company in the same or similar circumstances would have provided with respect to the danger. There were no warnings or instructions that communicate sufficient information on the dangers and safe use of the product taking into account the characteristics of the product, and/or the ordinary knowledge common to the physician who prescribes and the consumer who purchases the product, such as the Plaintiff.

(e) The metoclopramide manufactured and supplied by the DRUG COMPANY DEFENDANTS was further defective due to inadequate post-marketing warning or instruction because, after the DRUG COMPANY DEFENDANTS knew or should have known of the risks of injury

from Metoclopramide associated with long term use as commonly prescribed, they failed to promptly respond to and adequately warn about extrapyramidal side effects, among other adverse reactions.

365. The DRUG COMPANY DEFENDANTS knew, or in light of reasonably available scientific knowledge should have known, about the danger that caused the injuries for which Plaintiff seeks recovery. A reasonably competent physician who prescribed metoclopramide and a reasonably competent Plaintiff who consumed metoclopramide would not realize its dangerous condition.

366. The DRUG COMPANY DEFENDANTS knew or in light of reasonably available scientific knowledge should have known about the danger associated with use of metoclopramide that caused the damages for which Plaintiff seeks recovery.

367. The reasonably foreseeable use of metoclopramide, that is ingestion as treatment for gastritis/gastroesophageal reflux on a long term basis, involved substantial dangers not readily recognizable by the ordinary physician who prescribed metoclopramide or the patient, like Plaintiff, who consumed metoclopramide.

368. The DRUG COMPANY DEFENDANTS knew that the metoclopramide was to be prescribed by physicians and used by consumers without inspection for defects in the product or in any of

its components or ingredients and that metoclopramide was not properly prepared nor accompanied by adequate warnings of its dangerous propensities that were known or reasonably scientifically knowable at the time of distribution.

369. Plaintiff and Plaintiff's physicians did not know, nor had reason to know, at the time of the use of metoclopramide, or at any time prior to its use, of the existence of the above-described defects and inadequate warnings.

370. These defects caused serious injuries to Plaintiff when the product was used in its intended and foreseeable manner, and in the manner recommended by the DRUG COMPANY DEFENDANTS or in a non-intended manner that was reasonably foreseeable.

COUNT 2

BREACH OF EXPRESS WARRANTY BY WYETH AND SCHWARZ

371. Plaintiff repeats, reiterates, and realleges each and every allegation contained in this Complaint with the same force and effect as if fully set forth herein.

372. Defendants Wyeth and Schwarz's concealment and failure to warn through promotional statements and product literature expressly warranted to Plaintiff that its drug Reglan, metoclopramide and/or metoclopramide HCl was safe and capable of treating gastrointestinal

disorders, including diabetic gastroparesis, a long term chronic condition.

373. In response to these promises and express statements, Plaintiff and Plaintiff's physicians relied on such affirmations and warranties to Plaintiff through Plaintiff's physicians.

374. Reglan, metoclopramide and/or metoclopramide HCl do not conform to those express representations in light of recently discovered disclosures and information previously withheld by Wyeth and Schwarz. Wyeth and Schwarz's express warranty through its false statements failed to disclose and provide patient approval of the design, manufacturing and safety defects inherent in the drug.

375. Wyeth and Schwarz breached its warranty of Reglan, metoclopramide and/or metoclopramide HCl by continuing sales and marketing campaigns highlighting the safety of its drug, while it knew of the design, manufacturing and safety defects and risk of contracting a severe neurological disorder which was posed by the drug.

376. As a direct and proximate result of Wyeth and Schwarz's breach of its express warranty, Plaintiff suffered bodily and mental injury, harm, other compensable injury and economic losses, compensable through this Court.

COUNT 3

NEGLIGENCE AGAINST DRUG COMPANY DEFENDANTS

377. Plaintiff repeats, reiterates, and realleges each and every allegation contained in this Complaint with the same force and effect as if fully set forth herein.

378. DRUG COMPANY DEFENDANTS had a duty to exercise the care of an expert in all aspects of the formulation, manufacture, compounding, testing, inspection, packaging, labeling, distribution, marketing, and sale of Reglan, metoclopramide and/or metoclopramide HCl to insure the safety of its drug and to insure that the consuming public, including the Plaintiff and Plaintiff's physicians and agents, obtained accurate information and instructions for the safe use or non-use of this drug.

379. DRUG COMPANY DEFENDANTS breach of its duties proximately caused damages to Plaintiff. As a direct and proximate cause of DRUG COMPANY DEFENDANTS conduct, Plaintiff has suffered and will continue to suffer injury, harm, and economic loss as alleged herein, including a permanent and substantial physical disability, and expenses attributable to this disability. DRUG COMPANY DEFENDANTS breached their duty with the understanding customers and physicians would rely upon such actions when choosing DRUG COMPANY DEFENDANTS drug.

380. As manufacturers of prescription drug products, specifically Reglan, metoclopramide and/or metoclopramide HCl products, the DRUG COMPANY DEFENDANTS owed a duty toward foreseeable users of Reglan, metoclopramide and/or metoclopramide HCl products, including the Plaintiff, to exercise reasonable care to ensure that the Reglan, metoclopramide and/or metoclopramide HCl products they manufactured and/or distributed were reasonably safe for their ordinary and intended uses, and specifically, inter alias, to ensure through adequate testing, labeling, and otherwise, that physicians who would be likely to prescribe the products for their patients' use were adequately informed as to the potential effects of using the products in ordinary and foreseeable ways, in particular the risks inherent in such use.

381. Each of the DRUG COMPANY DEFENDANTS breached their duty, including the duty to assure that their products did not cause users to suffer from foreseeable unreasonably dangerous side effects and serious health problems, to members of the public who were expected to use their Reglan, metoclopramide and/or metoclopramide HCl products, including the Plaintiff, by failing to exercise reasonable care in testing the products for their effects in ordinary and foreseeable uses, including long term use, and in disseminating to physicians information concerning the effects of the product which was accurate, not misleading, and otherwise adequate to enable to physicians to

make informed choices concerning the reasonably safe use of the products.

382. DRUG COMPANY DEFENDANTS failed to exercise ordinary care in the manufacture, sale, testing, marketing, quality, assurance, quality control and/or distribution of the drugs into the stream of interstate commerce in that DRUG COMPANY DEFENDANTS knew or should have known that the drugs created a foreseeable high risk of unreasonable, dangerous side effects and health hazards.

383. The dangerous propensities of Reglan, metoclopramide and/or metoclopramide HCl products, as referenced above, were known or scientifically knowable, through appropriate research and testing, to the DRUG COMPANY DEFENDANTS at the time they distributed, supplied, or sold the products, and not known to ordinary physicians who would be expected to prescribe the drug for their patients, or their patients.

384. As manufacturers of prescription drug products, specifically Reglan, metoclopramide and/or metoclopramide HCl products, the DRUG COMPANY DEFENDANTS owed a duty toward foreseeable users of Reglan, metoclopramide and/or metoclopramide HCl products, including the Plaintiff, to exercise reasonable care to ensure that the Reglan, metoclopramide and/or metoclopramide HCl products they manufactured and/or distributed were reasonably safe for their ordinary and intended uses, and specifically, inter alia, to ensure

through adequate testing, labeling, and otherwise, that physicians who would be likely to prescribe the products for their patients' use were adequately informed as to the potential effects of using the products in ordinary and foreseeable ways, in particular the risks inherent in such use.

385. Each of the DRUG COMPANY DEFENDANTS breached their duty towards members of the public who were expected to use their Reglan, metoclopramide and/or metoclopramide HCl products, including the Plaintiff, by failing to exercise reasonable care in testing the products for their effects in ordinary and foreseeable uses, including long term use, and in disseminating to physicians information concerning the effects of the product which was accurate, not misleading, and otherwise adequate to enable to physicians to make informed choices concerning the reasonably safe use of the products.

386. The information the DRUG COMPANY DEFENDANTS disseminated to physicians concerning their Reglan, metoclopramide and/or metoclopramide HCl products was, in fact, inaccurate, misleading, and otherwise inadequate, as described above.

387. As a proximate result, Plaintiff suffered grievous bodily injuries and consequent economic and other losses when Plaintiff ingested, as prescribed, Reglan, metoclopramide and/or metoclopramide HCl, which had been developed, manufactured, labeled, marketed,

distributed, promoted and/or sold, either directly or indirectly, by DRUG COMPANY DEFENDANTS through third parties or related entities.

388. At all times mentioned in this Complaint, the DRUG COMPANY DEFENDANTS had a duty to properly manufacture, compound, test, inspect, package, label, distribute, market, examine, maintain, supply, provide proper warnings, and prepare for use and sell metoclopramide.

389. The DRUG COMPANY DEFENDANTS knew or should have known that use of metoclopramide created an unreasonable risk as a result of its design, testing, and/or manufacturing, including an unreasonable risk of central nervous system side effects, depression, akathesia, akinesia, tardive dyskinesia, tardive dystonia, visual disturbances and/or interference with drug metabolism, especially in female patients diagnosed with diabetes mellitus and more particularly in patients who are poor metabolizers of metoclopramide.

390. The DRUG COMPANY DEFENDANTS were negligent, and breached duties owed to Plaintiff with respect to metoclopramide in one or more of the following respects:

(a) Despite knowledge of hazards and knowledge that the product was frequently prescribed for long term use, they failed to accompany the product with adequate warnings and instructions

regarding the adverse and long lasting side effects associated with the use of metoclopramide and particularly with foreseeable long term use;

(b) They failed to conduct adequate testing;

(c) Despite knowledge of hazards, they failed to conduct adequate post-marketing surveillance to determine the safety of the product;

(d) Despite knowledge of hazards, they failed to adequately warn Plaintiff's physicians or Plaintiff that the use of metoclopramide could result in depression with suicidal ideation, akathesia, akinesia, tardive dyskinesia, tardive dystonia, visual disturbances and interferences with drug metabolism; and

(e) Despite the fact that the Drug Company Defendants knew or should have known that metoclopramide caused unreasonably dangerous side effects, they failed to adequately disclose the known or knowable risks associated with metoclopramide as set forth above; they willfully and deliberately failed to adequately disclose these risks, and in doing so, acted with a conscious disregard of Plaintiff's safety or welfare.

391. As a result of the negligence of the DRUG COMPANY DEFENDANTS and their willful and wanton misconduct, metoclopramide was

prescribed to Plaintiff for long term use and was used long term by Plaintiff, thereby causing Plaintiff to sustain reasonably foreseeable serious and permanent damages and injuries as alleged in this Complaint.

392. The negligence and the willful and wanton misconduct of the DRUG COMPANY DEFENDANTS was a proximate cause of Plaintiff's harm and injuries that Plaintiff has suffered and will continue to suffer as previously described.

393. In the alternative, DRUG COMPANY DEFENDANTS acts of omissions and concealment of material facts of the design and manufacturing defects were made with the understanding patients and physicians would rely upon such statements when choosing DRUG COMPANY DEFENDANT'S drug. Furthermore, the economic damages and physical harm caused by DRUG COMPANY DEFENDANT'S conduct would not have occurred had DRUG COMPANY DEFENDANTS exercised the high degree of care imposed upon it and Plaintiff therefore plead the doctrine of *res ipsa loquitur*.

394. Plaintiff repeats, reiterates, and realleges each and every allegation contained in this Complaint with the same force and effect as if fully set forth herein.

COUNT 4

MISREPRESENTATION BY OMISSION

395. Plaintiff repeats, reiterates, and realleges each and every allegation contained in this Complaint with the same force and effect as if fully set forth herein.

396. DRUG COMPANY DEFENDANTS misrepresented the soundness and reliability of their drug to physicians and the general public through promotional and marketing campaigns. It misrepresented that Reglan, metoclopramide and/or metoclopramide HCl was safe and/or effective when used as instructed, when, in fact, it was dangerous to the health of patients. DRUG COMPANY DEFENDANTS continued these misrepresentations for an extended period of time, without disclosing material information.

397. DRUG COMPANY DEFENDANTS took advantage of the limited opportunity Plaintiff had to discover DRUG COMPANY DEFENDANTS strategic and intentional concealment of the design, manufacturing and safety defects in Reglan, metoclopramide and/or metoclopramide HCl.

398. At the time DRUG COMPANY DEFENDANTS promoted the drug at issue as safe and/or effective, DRUG COMPANY DEFENDANTS did not have adequate proof upon which to base such representations, and in fact, knew or should have known that drug was dangerous.

399. DRUG COMPANY DEFENDANTS concealed these design and manufacturing defects from the public by withholding information pertaining to the inherent design, manufacturing and safety defects and high risks of a severe and permanent neurological condition relating to DRUG COMPANY DEFENDANTS Reglan, metoclopramide and/or metoclopramide HCl drug and presenting the drug as sound and reliable.

400. DRUG COMPANY DEFENDANTS intentional misrepresentations and omissions were made willfully, wantonly or recklessly to the Plaintiff to induce purchase of DRUG COMPANY DEFENDANTS Reglan, metoclopramide and/or metoclopramide HCl drug over other drugs on the market.

401. DRUG COMPANY DEFENDANTS knew or should have known of the high risk Plaintiff would encounter by unwittingly agreeing to ingest DRUG COMPANY DEFENDANTS defective drug.

402. Defendants failed to exercise reasonable care and competence in obtaining and/or communicating information regarding the safe use of Reglan, metoclopramide and/or metoclopramide HCl and otherwise failed to exercise reasonable care in transmitting information to Plaintiff, Plaintiff's physician, and the public in general.

403. Defendants made the aforesaid representations in the course of Defendants business as

designers, manufacturers, and distributors of the drug at issue despite having no reasonable basis for their assertion that these representations were true and/or without having accurate or sufficient information concerning the aforesaid representations. Defendants were aware that, without such information, it could not accurately make the aforesaid representations.

404. At the time the aforesaid representations were made, Defendants intended to induce Plaintiff and/or Plaintiff's physicians to rely upon such representations.

405. Said representations were made with the intent to defraud and deceive Plaintiff and/or Plaintiff's physicians and with the intent to induce Plaintiff and/or Plaintiff's physicians to rely upon the statements and use of Reglan, metoclopramide and/or metoclopramide HCl.

406. Plaintiff and/or Plaintiff's physicians, at the time the representations were made, were unaware of their falsity and believed them to be true. In reasonable reliance thereon by Plaintiff and/or Plaintiff's physicians used Reglan, metoclopramide and/or metoclopramide HCl, and as a result, Plaintiff has suffered, and will continue to suffer, injury, harm and economic loss alleged herein.

407. As a direct and proximate result of reliance upon DRUG COMPANY DEFENDANTS misrepresentations, Plaintiff has suffered and will continue to suffer injury, harm, and

economic loss as alleged herein, including a permanent and substantial physical disability, and expenses attributable to this disability.

COUNT 5

NEGLIGENCE

AS AGAINST DEFENDANT WYETH

408. Plaintiff repeats, reiterates, and realleges each and every allegation contained in this Complaint with the same force and effect as if fully set forth herein.

409. As set forth above, Wyeth and its predecessors falsely and fraudulently represented to Plaintiff's physicians, and through them to Plaintiff and members of the general public, that Reglan/metoclopramide was safe for use to treat gastritis/gastroesophageal reflux and that central nervous system side effects and extrapyramidal symptoms were comparatively rare. These representations were, in fact, false. The true facts were that Reglan/metoclopramide was not safe for that purpose and was, in fact, dangerous to the health and body of Plaintiff.

410. Wyeth and its predecessors made other representations about the safety and efficacy of Reglan/metoclopramide, and its minimal side effects all as set forth above and incorporated here by reference.

411. These representations were in fact, false. The true facts were that Reglan/metoclopramide

causes central nervous system side effects, and extrapyramidal symptoms, among other side effects, far more frequently than represented, and Wyeth and its predecessors did not disclose or warn physicians about the actual prevalence of known side effects of Reglan/metoclopramide, particularly when Reglan/metoclopramide is used on a long term basis or when used in patients who are poor metabolizers of metoclopramide, all of which were foreseeable. Wyeth and its predecessors misrepresented the safety of Reglan/metoclopramide and withheld warnings of the known side effects of Reglan/metoclopramide when used as commonly prescribed by physicians as specifically required by 21 C.F.R. § 201.128.

412. When Wyeth and its predecessors made these representations, they knew that they were false. Wyeth made these representations with the intent to defraud and deceive Plaintiff's physicians and through them to defraud and deceive Plaintiff and with the intent to induce Plaintiff and Plaintiff physicians to act in the manner alleged in this Complaint that is to use Reglan/metoclopramide as pharmaceutical treatment for gastritis/gastroesophageal reflux for a period of time that far exceeded the FDA's approved indicated duration of use.

413. At the time Wyeth and its predecessors made the above described representations and at the time Plaintiff and Plaintiff physicians took the actions alleged in this Complaint, Plaintiff and Plaintiff's physicians were ignorant of the falsity of the representations and reasonably believed

them to be true. In reliance upon the representations, Plaintiff's physicians were induced to and did prescribe Reglan/metoclopramide as described in this Complaint and Plaintiff did use Reglan/metoclopramide as described in this Complaint.

414. If Plaintiff's physicians had known the actual facts they would not have prescribed Reglan/metoclopramide in the manner that they prescribed it and Plaintiff would not have taken Reglan/metoclopramide in the way that it was prescribed.

415. The reliance of Plaintiff and Plaintiff's physicians upon the representations of Wyeth and its predecessors was justified because the representations were made by individuals and entities that appeared to be in the position to know the true facts.

416. As a proximate result of the fraud and deceit of Wyeth and its predecessors, Plaintiff sustained the injuries and damages described in this Complaint.

417. In doing the acts alleged in this Complaint, Wyeth and its predecessors acted with oppression, fraud, and malice and Plaintiff is therefore entitled to punitive damages to deter Wyeth and others from engaging in similar conduct in the future. This wrongful conduct was done with the advance knowledge, authorization, or ratification of an officer, director, or managing agent of each of Wyeth and its predecessors.

COUNT 6

NEGLIGENT MISREPRESENTATION

418. Plaintiff repeats, reiterates, and realleges each and every allegation contained in this Complaint with the same force and effect as if fully set forth herein.

419. DRUG COMPANY DEFENDANTS, WYETH, WYETH, INC., and SCHWARZ PHARMA owed a duty in all of their several undertakings, including the dissemination of information concerning Reglan, metoclopramide and/or metoclopramide HCl, to exercise reasonable care to ensure that they did not, in those undertakings, create unreasonable risks of personal injury to others.

420. DRUG COMPANY DEFENDANTS, WYETH, WYETH, INC., and SCHWARZ PHARMA disseminated to physicians, through package inserts, the publication of a PDR monograph, and otherwise, information concerning the properties and effects of Reglan, metoclopramide and/or metoclopramide HCl, with the intention that physicians would rely upon that information in their decisions concerning the prescription of drug therapy for their patients.

421. It is the public policy of the United States and of this state, as reflected in the Hatch-Waxman Act and the laws and regulations of the State of Minnesota to encourage the availability of cheaper, generic drug products that are

therapeutically equivalent name brand products and to encourage the substitution, as appropriate, of such generic products for name brand products in patients' medical therapy.

422. DRUG COMPANY DEFENDANTS, WYETH, WYETH, INC., and SCHWARZ PHARMA, as prescription drug manufacturers and/or distributors, knew or ought to have realized that so-called "drug product selection laws," enacted in every state, including this state, authorize or require a prescription for a drug identified by product brand name or by generic name to be filled, subject to certain limited exceptions, with a generic drug product that is therapeutically equivalent to the name brand drug product.

423. DRUG COMPANY DEFENDANTS, WYETH, WYETH, INC., and SCHWARZ PHARMA, as prescription drug manufacturers and/or distributors, knew or ought to have realized that the manufacturers and/or distributors of generic products, as a custom, to either ensure or give the impression that the information contained in the package inserts accompanying their own generic prescription drug products is accurate, complete, not misleading, and otherwise adequate, typically and simply copy verbatim, for those package inserts, the therapeutically relevant content of the package insert for the name brand prescription drug product, for which the generic products are therapeutic equivalents; and, further, that the manufacturers of the counterpart generic products typically rely upon the marketing

efforts of the name brand manufacturer to generate sales of their own products.

424. DRUG COMPANY DEFENDANTS, WYETH, WYETH, INC., and SCHWARZ PHARMA, knew or ought to have realized that physicians, to obtain basic information about the properties and effects of a drug or drug product that is available in both name brand and generic formulations, commonly and typically consult the information disseminated by the manufacturer/distributor of name brand product, in PDR monographs or otherwise, and rely upon that information in their decisions concerning the prescribing of those products for their patients, whether by brand name or generic name, and that the patients are likely to receive and ingest, per those prescriptions, one or more generic products that are therapeutically equivalent to the name brand product.

425. DRUG COMPANY DEFENDANTS, WYETH, WYETH, INC., and SCHWARZ knew or ought to have realized, specifically, that physicians, in weighing the potential benefits and potential risks of using Reglan, metoclopramide and/or metoclopramide HCl products, whether name brand or generic or either, and in writing prescriptions for either "Reglan" or "metoclopramide," would rely upon information disseminated to them by the manufacturer of the name brand drug product, regardless of whether the prescriptions might be filled with either the name brand product, Reglan, or generic Reglan, metoclopramide and/or

metoclopramide HCl products, and that many patients, in accordance with those prescriptions, would be likely to ingest generic Reglan, metoclopramide and/or metoclopramide HCl products.

426. DRUG COMPANY DEFENDANTS, WYETH, WYETH, INC., and SCHWARZ, knew or ought to have realized that patients receiving prescriptions for Reglan or generic Reglan, metoclopramide and/or metoclopramide HCl written in reliance upon information they disseminated as the manufacturer/distributor of Reglan, the name brand Reglan product, would be placed in peril of grievous personal injury if the information thus disseminated and relied upon was materially inaccurate, misleading, or otherwise false.

427. DRUG COMPANY DEFENDANTS, WYETH, WYETH, INC., AND SCHWARZ, and its predecessors in interest, failed to exercise reasonable care to ensure that the information they disseminated to physicians concerning the properties and effects of Reglan, metoclopramide and/or metoclopramide HCl and Reglan was accurate and not misleading, and as a result disseminated information to physicians that was negligently and materially inaccurate, misleading, and false.

428. As a proximate and foreseeable result of this negligence on the part of DRUG COMPANY DEFENDANTS, WYETH, WYETH, INC., and SCHWARZ, the Plaintiff suffered grievous bodily injury and consequent economic and

other loss, as described above, when Plaintiff's physician, in reasonable reliance upon the negligently inaccurate, misleading, and false information disseminated by said Defendants, and their predecessors in interest, and believing the information to be true, prescribed for the Plaintiff the use of Reglan, metoclopramide and/or metoclopramide HCl for a prolonged and unwarranted period of time and Plaintiff ingested, per those prescriptions, Reglan, metoclopramide and/or metoclopramide HCl products, leading to Plaintiff's toxic overexposure to Reglan, metoclopramide and/or metoclopramide HCl.

COUNT 7

NEGLIGENT MISREPRESENTATION

AS AGAINST DEFENDANT WYETH AND DEFENDANT SCHWARZ

429. Plaintiff repeats, reiterates, and realleges each and every allegation contained in this Complaint with the same force and effect as if fully set forth herein.

430. Wyeth and Schwarz had actual knowledge of facts which demonstrated that representations in the Reglan package insert, the PDR monograph for Reglan and literature that they distributed concerning Reglan/metoclopramide to physicians were false and misleading. Wyeth and Schwarz had an absolute duty to disclose the true facts regarding the safety of Reglan to physicians and their patients, pharmacists, and

the generic metoclopramide industry, which they negligently failed to do. Furthermore, Wyeth and Schwarz had a duty to ensure that they had a reasonable basis for making the representations described above, to exercise reasonable care in making those representations, to accurately make those representations, and to not make misrepresentations, all of which they negligently failed to do.

431. Important information regarding metoclopramide's risks was in the exclusive control of Wyeth and Schwarz and was exclusively known by them. As part of their business and in the furtherance of their own interests, Wyeth and Schwarz disseminated information regarding metoclopramide to physicians and their patients, pharmacists and the generic metoclopramide industry and did so knowing that the safety of metoclopramide users depended on the accuracy of that information. Further, Wyeth and Schwarz knew and expected that recipients of that information would rely on it, that they would take action based upon it, that individuals would be put in peril by such action and that those individuals would suffer physical harm as a result.

432. Wyeth and Schwarz expressly and/or impliedly represented to Plaintiff, Plaintiff's physicians, pharmacists, the generic metoclopramide industry and members of the general public that Reglan/metoclopramide was safe for use to treat nausea and/or esophageal reflux for durations of use that exceeded the 12 week duration

indicated in Wyeth and Schwarz's package inserts and in the PDR. The representations by Wyeth and Schwarz and the lack of them were, in fact, false. The true facts were that Reglan/metoclopramide was not safe for use in the manner in which it was prescribed and was, in fact, dangerous to the health and body of Plaintiff.

433. Wyeth and Schwarz made the above described representations with no reasonable grounds for believing them to be true. Wyeth and Schwarz did not have accurate or sufficient information concerning these representations and they failed to exercise reasonable care both in ascertaining the accuracy of the information contained in those representations and in communicating the information. Further, Wyeth and Schwarz were aware that without such information they could not accurately make the above described representations.

434. The above misrepresentations or omissions were made to Plaintiff, Plaintiff's physicians, pharmacists, the generic pharmaceutical industry and the general public, all of whom justifiably and foreseeably relied on those representations or omissions. Plaintiff would not have suffered Plaintiff injuries but for the above misrepresentations or omissions. Wyeth and Schwarz's misrepresentations or omissions were a cause in fact and a proximate cause of Plaintiff's damages.

COUNT 8

FRAUD BY CONCEALMENT

435. Plaintiff repeats, reiterates, and realleges each and every allegation contained in this Complaint with the same force and effect as if fully set forth herein.

436. The DRUG COMPANY DEFENDANTS, with the intention of deceiving physicians and their patients, and to induce physicians to prescribe, and their patients to ingest, Reglan, metoclopramide and/or metoclopramide HCl products for prolonged periods of time, informed physicians, through package inserts and otherwise, that exposure to Reglan, metoclopramide and/or metoclopramide HCl can lead to Tardive Dyskinesia and other ESP, that the risk is "believed" to increase with duration of therapy and total cumulative dose, and that therapy for longer than twelve (12) weeks "cannot be recommended," but knowingly concealed from the physicians material facts bearing on the interpretation of those disclosures, including the fact that earlier false information, disseminated by A.H. ROBINS COMPANY, and representing long term Reglan, metoclopramide and/or metoclopramide HCl therapy to be reasonably safe, was unscientific and false; that Reglan, metoclopramide and/or metoclopramide HCl is a neuroleptic agent and dopamine antagonist, which can be expected to lead to Tardive Dyskinesia and other ESP with approximately the same high frequency, particularly in longer term use, as other

neuroleptic drugs; that epidemiological studies have consistently confirmed this expectation; and that the treatment of chronic or intermittent gastroesophageal reflux and/or diabetic gastroporesis, and/or other gastric disorders with Reglan, metoclopramide and/or metoclopramide HCl products for longer than 12 weeks is unlikely to be reasonably safe.

437. The Plaintiff's physician, in reliance upon the information disseminated by the DRUG COMPANY DEFENDANTS, and without knowledge of the undisclosed and knowingly concealed facts, determined that the benefits of prolonged Reglan, metoclopramide and/or metoclopramide HCl therapy outweighed the risks for their patient, the Plaintiff, and prescribed a prolonged course of therapy for Plaintiff with Reglan, metoclopramide and/or metoclopramide HCl products.

438. As a proximate and foreseeable result of this knowing and fraudulent concealment of material facts on the part of the DRUG COMPANY DEFENDANTS, Plaintiff suffered grievous bodily injury and consequent economic and other loss when Plaintiff's physician, in reliance upon the information disseminated by the DRUG COMPANY DEFENDANTS, and in ignorance of the facts concealed from them in those disseminations, prescribed for the Plaintiff the use of Reglan, metoclopramide and/or metoclopramide HCl for a prolonged and unwarranted period of time and Plaintiff ingested, per those prescriptions, Reglan, metoclopramide and/or metoclopramide HCl

products, leading to Plaintiff's toxic overexposure to Reglan, metoclopramide and/or metoclopramide HCl.

COUNT 9

VIOLATION OF MINNESOTA CONSUMER PROTECTION ACT

439. Plaintiff repeats, reiterates, and realleges each and every allegation contained in this Complaint with the same force and effect as if fully set forth herein.

440. By reason of the conduct as alleged herein, DRUG COMPANY DEFENDANTS violated the Minnesota Consumer Protection Act, by knowingly and intentionally inducing Plaintiff to use the drugs through the use of false and/or misleading advertising, representations and statements. The products failed to perform as represented and advertised, and in fact were unsafe.

441. The DRUG COMPANY DEFENDANTS induced the Plaintiff and Plaintiff's physician, through the use of false and/or misleading advertising, representations, and statements, as described above, to use and/or prescribe Reglan, metoclopramide and/or metoclopramide HCl products which they manufactured and/or distributed and sold, all in violation of the Minnesota Consumer Protection Act which proscribes, among other things:

a. Engaging in unfair trade practices as defined in the statute by making false and misleading oral and written statements that have the capacity, tendency or effect of deceiving or misleading consumers;

b. Engaging in unfair trade practices as defined in the statute by making representations that their products had an approval, characteristic, ingredient, use or benefit which they did not have, including but not limited to statements concerning the health consequences of the use of drugs;

c. Engaging in unfair trade practices as defined in the statute by failing to state material facts, the omission of which deceive or tend to deceive, including but not limited to, facts relating to the health consequences of the use of these drugs; and

d. Engaging in unfair trade practices as defined in the statute through deception, fraud, misrepresentation, and knowing concealment, suppression and omission of material facts with the intent that consumers rely upon the same in connection with the use and continued use of the drugs.

442. As a direct and proximate result of DRUG COMPANY DEFENDANTS statutory violations, plaintiff used the drugs as prescribed, which Plaintiff would not have used had DRUG COMPANY DEFENDANTS not issued false and/or misleading advertising, representations and statements.

443. By reason of such violations and pursuant to the laws and regulations of this state, Plaintiff is entitled to recover all of the monies paid for the products; to be compensated for the cost of medical care arising out of the use of the products; together with any and all actual damages recoverable under the law including, but not limited to, past medical expenses, past wage loss, past pain, suffering, disability and emotional distress.

444. In addition, Plaintiff is entitled to recover fees and disbursements, including costs of investigation, reasonable attorneys' fees, and any other equitable relief as determined by this Court.

445. Defendant WYETH (including A.H. Robins Company, Inc., prior to its merger into WYETH, and as WYETH thereafter) has marketed Reglan to physicians in a manner calculated to increase sales of the drug and resultant profits to the drug company at the expense of and in conscious disregard for the health and safety of those who, through over-prescription of the drug at excessive dosage and/or for excessive periods of time and/or for patients for whom safer effective alternative treatments existed, consequently develop Tardive Dyskinesia and other extrapyramidal symptoms (EPS).

446. In doing the wrongful acts alleged in this Complaint, WYETH, WYETH, INC., AND SCHWARZ, acted with oppression, fraud, and malice, evincing a willful, wanton, and conscious disregard for the rights, health, and safety of

patients, including the Plaintiff, who would be expected to be induced, by that conduct, to ingest unwarranted amounts of Reglan, metoclopramide and/or metoclopramide HCl for prolonged and unwarranted periods of time, leading to grievous, debilitating, and potentially permanent personal injury.

447. Some or all of the other DRUG COMPANY DEFENDANTS, as a result of their participation as DRUG COMPANY DEFENDANTS in previous litigation concerning Reglan and other Reglan, metoclopramide and/or metoclopramide HCl products, received clear notice of WYETH'S suppression of important safety information concerning Reglan, metoclopramide and/or metoclopramide HCl and their products, yet despite this notice chose to ignore the information and join consciously in the suppression.

448. The conduct of the DRUG COMPANY DEFENDANTS, and each of them, undertaken consciously and with notice, evinces a willful, wanton, and conscious disregard for the rights, healthy, and safety of patients, including the Plaintiff, who would be expected to be induced, by that conduct, to ingest unwarranted amounts of Reglan, metoclopramide and/or metoclopramide HCl for prolonged and unwarranted periods of time, leading to grievous, debilitating, and potentially permanent personal injury.

449. As a direct and proximate result of the wrongful acts of the DRUG COMPANY DEFENDANTS Plaintiff developed severe Tardive Dyskinesia, suffered irreparable nerve damage and bodily injury, suffered and will continue to suffer great pain of body and mind, suffered and will continue to suffer great embarrassment and humiliation, suffered and will continue to suffer permanent impairment to Plaintiff's earnings capacity, has incurred and will continue to incur great expenses for medical treatment of Plaintiff's injuries, has suffered and will continue to suffer the loss of enjoyment of life and has been otherwise damaged to be further shown by the evidence.

COUNT 10

FRAUD BY CONCEALMENT

AS AGAINST DEFENDANT WYETH AND DEFENDANT SCHWARZ

450. Plaintiff repeats, reiterates, and realleges each and every allegation contained in this Complaint with the same force and effect as if fully set forth herein.

451. At all times mentioned in this Complaint, Wyeth and its predecessors had the duty and obligation to disclose to Plaintiff and to Plaintiff's physicians the true facts concerning Reglan/ metoclopramide, that is, that Reglan/metoclopramide was dangerous and defective and how likely it was to cause serous consequences to users, including injuries as

described in this Complaint, and the true level of risk involved in prescribing Reglan/ metoclopramide for the purposes indicated. Wyeth and its predecessors made the affirmative representations set forth above to Plaintiff, Plaintiff's prescribing physicians, and the general public prior to the day Plaintiff was first prescribed and used Reglan/ metoclopramide while concealing the material facts set forth below.

452. At all times mentioned in this Complaint, Wyeth and its predecessors had the duty and obligation to disclose to Plaintiff and to Plaintiff's physicians the true facts concerning Reglan/ metoclopramide that is that long term use and exposure could cause central nervous system side effects, depression with suicidal ideation, akathesia, akinesia, tardive dyskinesia and tardive dystonia. At all times mentioned in this Complaint, Wyeth and its predecessors intentionally, willfully and maliciously concealed or suppressed the facts set forth above from Plaintiff's physicians, and therefore from Plaintiff, with the intent to defraud as alleged in this Complaint.

453. At all times mentioned in this Complaint, neither Plaintiff nor Plaintiff's physicians were aware of the facts set forth above. Had they been aware of those facts, they would not have acted as they did, that is, would not have utilized Reglan/metoclopramide in the treatment of Plaintiff's gastritis/gastro-esophageal reflux for periods of time that exceeded 12 weeks duration.

454. As a proximate result of the concealment or suppression of the facts set forth above, Plaintiff was prescribed and took Reglan/metoclopramide and subsequently became ill, thereby sustaining the injuries and damages as set forth in this Complaint.

455. In doing the acts alleged in this Complaint, Wyeth and its predecessors acted with oppression, fraud, and malice, and Plaintiff is therefore entitled to punitive damages in an amount reasonably related to Plaintiff's actual damages and to Wyeth's wealth, and sufficiently large to be an example to others and to deter Wyeth and others from engaging in similar conduct in the future.

COUNT 11

BREACH OF IMPLIED WARRANTIES

456. Plaintiff repeats, reiterates, and realleges each and every allegation contained in this Complaint with the same force and effect as if fully set forth herein.

457. The DRUG COMPANY DEFENDANTS knew that most physicians who prescribed Reglan, metoclopramide and/or metoclopramide HCl were not aware the drug is a dopamine antagonist and/or a neuroleptic agent, which is just as likely to cause serious extrapyramidal side effects as other dopamine antagonists and/or other neuroleptic drugs. The DRUG COMPANY DEFENDANTS also knew that the risks of potentially irreversible neurological side

effects when Reglan, metoclopramide and/or metoclopramide HCl is used long term were much greater than most physicians realized. By failing to give adequate warnings about the dopamine antagonist and/or neuroleptic properties of Reglan, metoclopramide and/or metoclopramide HCl and the risk of long term use that is associated with those properties, the DRUG COMPANY DEFENDANTS breached implied warranties of merchantability and fitness for the ordinary use of Reglan, metoclopramide and/or metoclopramide HCl.

458. At all times mentioned in this Complaint, the DRUG COMPANY DEFENDANTS manufactured, compounded, packaged, distributed, recommended, merchandised, advertised, promoted, supplied and sold Reglan, metoclopramide and/or metoclopramide HCl and prior to the time it was used by Plaintiff, the DRUG COMPANY DEFENDANTS impliedly warranted to Plaintiff and to Plaintiff's physicians that the product was of merchantable quality and safe and fit for the use for which it was intended.

459. Plaintiff relied on the skill and judgment of the DRUG COMPANY DEFENDANTS in using Reglan, metoclopramide and/or metoclopramide HCl.

460. Reglan, metoclopramide and/or metoclopramide HCl was unsafe and unfit for its intended use, nor was it of merchantable quality, as warranted by the DRUG COMPANY DEFENDANTS, in that it had very dangerous

propensities when put to its intended use and would cause severe injury to the user. Reglan, metoclopramide and/or metoclopramide HCl was not properly prepared nor accompanied by adequate warnings of its dangerous propensities that were either known or reasonably scientifically knowable at the time of distribution. As a result, Reglan, metoclopramide and/or metoclopramide HCl proximately caused Plaintiff to sustain damages and injuries as alleged in this Complaint by virtue of causing Plaintiff's illness.

461. After Plaintiff was made aware of Plaintiff's injuries as a result of Reglan, metoclopramide and/or metoclopramide HCl, notice was duly given to the DRUG COMPANY DEFENDANTS of the breach of the above described warranties.

COUNT 12

STRICT JOINT AND SEVERAL LIABILITY

462. Plaintiff repeats, reiterates, and realleges each and every allegation contained in this Complaint with the same force and effect as if fully set forth herein.

463. By virtue of their individual and collective acts and omissions, Defendants are jointly and severally liable to Plaintiff as such acts and omissions have proximately caused Plaintiff to suffer a single indivisible injury for which each Defendant is responsible.

COUNT 13

CONSTRUCTIVE FRAUD

464. Plaintiff repeats, reiterates, and realleges each and every allegation contained in this Complaint with the same force and effect as if fully set forth herein.

465. DRUG COMPANY DEFENDANTS, while in possession of unique and pertinent information involving the safety and reliability of Reglan, metoclopramide and/or metoclopramide HCl as sound and failed to warn of the drugs inherent design, safety and manufacturing defects. DRUG COMPANY DEFENDANTS suppressed this information and continued sales and marketing of their drug to the general public. DRUG COMPANY DEFENDANTS knew or should have known Plaintiff had no means, other than DRUG COMPANY DEFENDANTS full, accurate, and objective disclosure, of obtaining the relevant information.

466. Through its unique knowledge and expertise regarding the affected nature of Reglan, metoclopramide and/or metoclopramide HCl and through its statements to physicians and their patients in advertisement, promotional materials, and other communications, DRUG COMPANY DEFENDANTS professed and affirmed to Plaintiff its knowledge of the truth of the representation that the drug at issue was safe for its intended use and was free from design, safety and manufacturing defects.

467. DRUG COMPANY DEFENDANTS misrepresentations and omissions were made intentionally to induce Plaintiff to purchase DRUG COMPANY DEFENDANTS drug in order to reap the high profit margin relating to DRUG COMPANY DEFENDANTS

468. DRUG COMPANY DEFENDANTS conduct took unconscionable advantage of its dominant position of knowledge, engaging in constructive fraud in its relationship with Plaintiff. Misled by this veil of fraud, Plaintiff reasonably relied on DRUG COMPANY DEFENDANTS representations.

469. As a result, Plaintiff has suffered and will continue to suffer injury, harm, and economic loss as alleged herein, including a permanent and substantial physical disability, and expenses attributable to this disability.

COUNT 14

INTENTIONAL INFLICTION OF EMOTIONAL DISTRESS

470. Plaintiff repeats, reiterates, and realleges each and every allegation contained in this Complaint with the same force and effect as if fully set forth herein.

471. Through intentional, reckless, and extreme conduct DRUG COMPANY DEFENDANTS knowingly denied Plaintiff adequate opportunity in measuring the level of risk related to DRUG COMPANY DEFENDANTS Reglan,

metoclopramide and/or metoclopramide HCl drug. By withholding information of known design and manufacturing defects and concealing those fatal problems, DRUG COMPANY DEFENDANTS created a false sense of security for Plaintiff, who assumed reasonable safety with DRUG COMPANY DEFENDANTS drug Reglan, metoclopramide and/or metoclopramide HCl.

472. DRUG COMPANY DEFENDANTS conduct of intentional omission, concealment, and failure to warn of the design and manufacturing defects caused Plaintiff to suffer injury, harm, and economic loss as alleged herein, including a permanent and substantial physical disability, and expenses attributable to this disability.

473. The injuries described above entitle Plaintiff to compensatory damages and equitable and declaratory relief, along with all appropriate damages according to proof.

COUNT 15

NEGLIGENT INFLICTION OF EMOTIONAL DISTRESS

474. Plaintiff repeats, reiterates, and realleges each and every allegation contained in this Complaint with the same force and effect as if fully set forth herein.

475. DRUG COMPANY DEFENDANTS intentionally and willfully failed to disclose or warn of the inherent risks and defects to its

physicians and patients. DRUG COMPANY DEFENDANTS enforced its negligent conduct through manufacturing, marketing, and selling its defective drug to Plaintiff, while knowingly concealing design, manufacturing and safety defects, and misrepresenting the risks of severe side effects, quality, safety, and efficacy of the drug.

476. DRUG COMPANY DEFENDANTS willful conduct inflicted Plaintiff with severe emotional distress through Plaintiff=s subsequent illness, and permanent disability resulting from Reglan, metoclopramide and/or metoclopramide HCl.

477. DRUG COMPANY DEFENDANTS conduct of willful omission and concealment of design, manufacturing and safety defects in order to induce ingestion of the drug caused Plaintiff severe emotional distress.

478. As a direct result of DRUG COMPANY DEFENDANTS careless and negligent conduct, Plaintiff has suffered and will continue to suffer injury, harm, and economic loss as alleged herein, including a permanent and substantial physical disability, and expenses attributable to this disability.

VI. DAMAGES

479. As a direct and proximate result of the acts and omissions of the Defendants, Plaintiff ingested Reglan, which was causally related to and contributed to Plaintiff's development of the

permanent neurological disorder known as Tardive Dyskinesia.

480. As a direct and proximate result of the acts and omissions of the Defendants, Plaintiff has suffered extreme emotional distress, anguish, physical and mental suffering, loss of the ability to control Plaintiff's facial expressions, mouth, tongue and jaw, and has rendered Plaintiff's physically incapacitated.

481. As a direct and proximate result of the acts and omissions of the Defendants, Plaintiff experiences extreme embarrassment, shame, anguish, anxiety, and has a sustained a loss of enjoyment of life.

482. Plaintiff seeks the recovery for past and future special damages, which includes medication, doctor, rehabilitation, therapy, and other assisted living and nursing care and Plaintiff also seeks general damages in the amount to be determined for the wrongful conduct of each separate and individual Defendant.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff prays for relief against Defendants as follows:

483. For judgment for damages sufficient to compensate for damages in excess of $75,000.00, including but not limited to past, present, and future economic expenditures in connection with DRUG COMPANY DEFENDANTS Reglan,

metoclopramide and/or metoclopramide HCl drug;

484. For compensatory damages according to proof;

485. For all applicable statutory remedies provided by law in Minnesota that assert liability for DRUG COMPANY DEFENDANTS wrongdoings and improper conduct;

486. For a disgorgement of profits;

487. For prejudgment interest, as permitted by law;

488. For reasonable costs, including attorneys fees as permitted by law; and

489. For all other just and proper relief.

Plaintiff seeks a trial by jury on all issues.

Respectfully Submitted,

GOLDENBERG & JOHNSON, PLLC

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ACKNOWLEDGMENT

The undersigned hereby acknowledges that costs, disbursements, and reasonable attorneys and witness fees may be awarded pursuant to Minn. Stat. §549.21, Subd. 2, to the parties against whom the allegations in this pleading are asserted.

Dated: 9/7/07

By /s/Michael K. Johnson
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UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MINNESOTA

CASE NO.: 07-CV-3919 PJS/RLE

[Filed November 13, 2007]

GLADYS MENSING,

Plaintiff,

vs.

WYETH, INC. (d/b/a WYETH), SCHWARZ PHARMA, INC.; PLIVA, INC.; TEVA PHARMACEUTICALS, USA, INC.; ALPHARMA, INC., d/b/a ALPHARMA PHARMACEUTICALS; UDL LABORATORIES, INC.; ACTAVIS ELIZABETH LLC; and PUREPAC PHARMACEUTICAL CO,, and the following fictitious party defendants (whether singular or plural, individual or corporate): No. 1, that entity which originally obtained permission from the U.S. Food and Drug Administration to market the drug branded Reglan; No. 2 that entity which obtained permission from the FDA to market the Reglan, metoclopramide and/or metoclopramide HCl ingested by Gladys Mensing; No. 3, that entity which originally manufactured and sold any Reglan which was ultimately ingested by Gladys Mensing; No. 4, that entity which originally manufactured and sold any Reglan, metoclopramide and/or metoclopramide HCl which was ultimately ingested by Gladys

Mensing; No. 5, that entity which marketed Reglan or generic metoclopramide and/or metoclopramide HCl,

Defendants.

DEFENDANT ACTAVIS-ELIZABETH, LLC'S ANSWER TO PLAINTIFF'S COMPLAINT

JURY TRIAL DEMANDED

Defendant, Actavis-Elizabeth, LLC (hereinafter Actavis), by and through counsel and for its Answer to Plaintiff Gladys Mensing's Complaint, states as follows:

PARTIES

1. Actavis is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraphs 1, 2, and 3. Therefore, Actavis denies the allegations in those paragraphs.

2. The allegations in paragraph 4 are definitional statements relating to other Defendants to which no response is necessary by this Defendant but to the extent that this paragraph alleges claims against this answering Defendant, such allegations are denied.

3. Actavis is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraphs 5-11. Therefore, Actavis denies the allegations in paragraphs 5-11.

4. In response to paragraph 12, Actavis denies that Purepac Pharmaceutical Co. is still in existence and answering further states that at one time when Purepac Pharmaceutical Co. was in existence Alpharma, Inc. was the parent corporation. Actavis admits that Alpharma, Inc. was and is a Delaware Corporation. Answering further, Defendant admits that Purepac Pharmaceutical Co. did manufacture and distribute metoclopramide but denies all remaining allegations of paragraph 12.

5. Actavis denies the allegations in paragraph 13.

6. In response to the allegations contained in paragraph 14 of Plaintiff's Complaint, Actavis admits that when Purepac Pharmaceutical Co. was in existence it did manufacture and distribute metoclopramide but denies all the remaining allegations in paragraph 14.

7. Actavis is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 15. Therefore, Actavis denies the allegations in paragraph 15.

8. In response to paragraph 16, Actavis denies that it is a New Jersey Corporation but admits that it manufactures and distributes metoclopramide and denies all the remaining allegations in paragraph 16.

9. Actavis is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 17. Therefore, Actavis denies the allegations in paragraph 16.

10. The allegations in paragraph 18 are definitional statements relating to other Defendants to which no response is necessary by this Defendant but to the extent that this paragraph alleges claims against this answering Defendant, such allegations are denied.

11. In response to paragraphs 19-22, Actavis admits that it currently manufactures and distributes metoclopramide and that Purepac Pharmaceutical Co. previously did so but denies the remaining allegations contained in these paragraphs.

VENUE AND JURISDICTION

12. Actavis is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 23. On that basis, Actavis denies the allegations in paragraph 23.

13. Actavis is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 24 as it relates to the other Defendants and denies the allegations as to itself.

FACTUAL BACKGROUND

14. Actavis is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraphs 25-33. Therefore, Actavis denies the allegations in those paragraphs.

15. Actavis denies the allegations in paragraph 34.

16. Actavis is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraphs 35-41. Therefore, Actavis denies the allegations in those paragraphs.

ALLEGATIONS

17. Actavis admits that tardive dyskinesia is a neurological disorder that can result in movement disorders and denies the remaining allegations in paragraph 42 for want of information, knowledge, and otherwise.

18. Actavis is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraphs 43-46. Therefore, Actavis denies the allegations in paragraphs 43-46.

19. The allegations in paragraphs 47-76 are not directed to this Defendant. To the extent they might be construed as such, Actavis denies all such allegations for want of information, knowledge, and otherwise.

20. The allegations in paragraph 77-133 are not directed to this Defendant. To the extent those allegations might be construed as such, Actavis denies all such allegations for want of information, knowledge, or otherwise.

21. Actavis denies the allegations in paragraphs 134 through 139 and specifically denies that it submitted an ANDA on metoclopramide.

22. In response to paragraph 140, Actavis admits that it currently markets metoclopramide and is obligated to follow FDA regulations which require its

label to parallel that of the brand name manufacturer and Actavis denies the remaining allegations of paragraphs 140.

23. Actavis denies all the allegations in paragraphs 141 through 152.

24. In response to paragraphs 153 to 171, Actavis admits that Defendant Purepac submitted an Abbreviated New Drug Application for metoclopramide and established the bioequivalency of its drug to the brand name drug and that it had a legal obligation to comply with all FDA regulations and was forced by applicable regulation to use exactly the same warning label approved by the brand name manufacturer. Actavis denies all the remaining allegations contained in paragraphs 153 to 171 not previously admitted for want of knowledge and information sufficient to form a belief as to the truth of these allegations.

25. In response to paragraphs 172 to 178, Actavis states a generic manufacturer of prescriptions drugs must comply with applicable FDA regulations including those that require that generic manufactures use the same label as the brand name manufacturer and denies all the remaining allegations of these paragraphs.

26. The allegations in paragraphs 179-209 are not directed to this Defendant. To the extent these allegations might be construed as such, Actavis denies all such allegations for want of information, knowledge, or otherwise.

27. Actavis denies all the allegations contained in paragraphs 210-215 directed to Actavis and is

without knowledge, information, or belief as to the accuracy of the allegations as directed to the other Defendants.

28. The allegations in paragraphs 216-219 are not directed to this Defendant. To the extent these allegations might be construed as such, Actavis denies all such allegations for want of information, knowledge, or otherwise.

29. Actavis denies the allegations in paragraph 220.

30. The allegations in paragraphs 221-231 are not directed to this Defendant. To the extent these allegations might be construed as such, Actavis denies all such allegations for want of information, knowledge, or otherwise.

31. Actavis denies all the allegations in paragraphs 232 and 233.

32. The allegations in paragraphs 234-235 are not directed to this Defendant. To the extent these allegations might be construed as such, Actavis denies all such allegations for want of information, knowledge, or otherwise.

33. Actavis denies all of the allegations in paragraphs 236-238.

34. The allegations in paragraphs 239-258 are not directed to this Defendant. To the extent these allegations might be construed as such, Actavis denies all such allegations for want of information, knowledge or otherwise.

35. Actavis denies the allegations in paragraph 259.

36. The allegations in paragraphs 260-315 are not directed to this Defendant. To the extent these allegations might be construed as such, Actavis denies all such allegations for want of information, knowledge, or otherwise.

37. Actavis denies the allegations in paragraphs 316 and 317 for want of information, knowledge, and otherwise.

38. The allegations contained in paragraph 318 are not directed to this Defendant. To the extent these allegations might be construed as such, Actavis denies all such allegations for want of information, knowledge, or otherwise.

39. In response to paragraph 319, Actavis states its duties are those prescribed by the FDA and otherwise denies the allegations.

40. Actavis denies all the allegations in paragraphs 320-350.

COUNT 1

41. Actavis admits that it marketed metoclopramide but denies the remaining allegations contained in paragraphs 351 to 370 of Plaintiff's Complaint as directed against it and denies the allegations as to the remaining Defendants for want of information, knowledge, and otherwise.

COUNT 2

42. The allegations in paragraphs 371 to 376 are not directed against this defendant and to the extent they might be deemed to be so directed, Actavis denies them.

COUNT 3

43. Actavis denies the allegations in paragraphs 377 to 394 as directed against it and denies the allegations as to other Defendants for want of information, knowledge, and otherwise.

COUNT 4

44. Actavis denies the allegations in paragraphs 395 to 407 of Plaintiff's Complaint and denies the allegations against the other Defendants for want of information, knowledge, and otherwise.

COUNT 5

45. The allegations contained in paragraphs 408 to 417 are not directed against Actavis and therefore no response in necessary but to the extent these allegations may be construed to allege claims against Actavis, these allegations are denied.

COUNT 6

46. Actavis admits that it was obligated to follow applicable federal regulations in regard to manufacture and distribution to metoclopramide and denies all remaining allegations contained in paragraphs 418 through 428 of Plaintiff's Complaint.

and denies the allegations in these paragraphs relating to the other Defendants for want of information, knowledge, and otherwise.

COUNT 7

47. The allegations contained in paragraphs 429 to 434 of Plaintiff's Complaint are not directed against this answering defendant and therefore no response in necessary, but to the extent they are deemed to be so, they are denied.

COUNT 8

48. Actavis denies the allegations contained in paragraphs 435 to 438 of Plaintiff's Complaint to the extent these paragraphs direct allegations against Actavis, and denies the allegations directed against the other Defendants for want of information, knowledge, or otherwise.

COUNT 9

49. Actavis denies the allegations contained in paragraphs 439 to 449 of Plaintiff's Complaint to the extent these paragraphs direct allegations against Actavis, and denies the allegations directed against the other Defendants for want of information, knowledge, or otherwise.

COUNT 10

50. The allegations contained in paragraphs 450 to 455 of Plaintiff's Complaint are not directed against Actavis and to the extent they may be deemed so, they are denied.

COUNT 11

51. Actavis denies the allegations contained in paragraphs 456 to 461 of Plaintiff's Complaint to the extent these paragraphs direct allegations against Actavis, and denies the allegations directed against the other Defendants for want of information, knowledge, or otherwise.

COUNT 12

52. Actavis denies the allegations contained in paragraphs 462 to 463 of Plaintiff's Complaint to the extent these paragraphs direct allegations against Actavis, and denies the allegations directed against the other Defendants for want of information, knowledge, or otherwise.

COUNT 13

53. Actavis denies the allegations contained in paragraphs 464 to 469 of Plaintiff's Complaint to the extent these paragraphs direct allegations against Actavis, and denies the allegations directed against the other Defendants for want of information, knowledge, or otherwise.

COUNT 14

54. Actavis denies the allegations contained in paragraphs 470 to 473 of Plaintiff's Complaint to the extent these paragraphs direct allegations against Actavis, and denies the allegations directed against the other Defendants for want of information, knowledge, or otherwise.

COUNT 15

55. Actavis denies the allegations contained in paragraphs 474 to 478 of Plaintiff's Complaint to the extent these paragraphs direct allegations against Actavis, and denies the allegations directed against the other Defendants for want of information, knowledge, or otherwise.

DAMAGES

56. Defendant denies the allegations contained in paragraphs 479 to 482 of Plaintiff's Complaint.

PRAYER FOR RELIEF

57. Defendant denies that Plaintiff is entitled to any of the relief sought in paragraphs 483 to 489 of Plaintiff's Complaint.

AFFIRMATIVE DEFENSES

58. Plaintiff's Amended Complaint fails to state a claim upon which relief may be granted.

59. Plaintiff's fraud claims are barred due to her failure to plead the circumstances constituting the alleged fraud with particularity as required by Fed. R. Civ. P. 9(b).

60. Plaintiff's Amended Complaint is barred for failure to join indispensable parties.

61. Plaintiff assumed the risk of her alleged damages.

62. Plaintiff, Gladys Mensing, was negligent and her negligence should be compared with that of the Defendants, which negligence is specifically denied, to reduce or bar her claims as set forth in Minnesota Statutes section 604.01.

63. Plaintiff's alleged damages were caused by her failure to exercise ordinary care to follow the advice, information, warnings and instructions provided with any product marketed by Actavis.

64. Plaintiff's alleged injuries and damages, if any, were the result of the misuse of the subject pharmaceutical product at issue. Defendant further alleges that if Plaintiff suffered injuries attributable to the Plaintiff's use of the subject pharmaceutical product at issue in this suit, which allegations are expressly denied, the injuries, if any, were solely caused and attributable to the unreasonable, unforeseeable and improper use of said pharmaceutical product by the Plaintiff and/or third parties.

65. Plaintiff's alleged damages were caused by the negligence or other fault of persons or entities other than Actavis who are not within the control of Actavis and for whom Actavis has no liability.

66. Plaintiff's alleged damages resulted from new and independent, unforeseeable, superseding and/or intervening causes unrelated to any conduct of, or product placed in the stream of commerce by, Actavis.

67. Plaintiff's alleged damages were the result of preexisting conditions unrelated to any conduct of, or product placed in the stream of commerce by, Actavis.

68. Actavis provided adequate and complete warnings to Plaintiff's prescribing physicians. Any claim made by Plaintiff for inadequate warnings accordingly is barred by the learned intermediary doctrine.

69. Reglan® and/or generic metoclopramide was designed, tested, manufactured, and marketed in conformance with the state of the scientific, medical and technological art and knowledge existing at the time of sale and, accordingly, Plaintiff's claims are barred.

70. Plaintiff's claims are barred, in whole or in part, because Actavis complied with all applicable statutes and with the requirements and regulations of the Food and Drug Administration and all of Plaintiff's claims are therefore barred, in whole or in part, by the Supremacy Clause of the United States Constitution, Article IV, clause 2, and the laws of the United States. Specifically, Plaintiff's failure to warn claims are preempted by federal food and drug regulations specifying that the warning language that can be used by generic manufacturers must be exactly the same as that approved by the FDA for use by the innovator manufacturer.

71. Plaintiff's claims are barred in whole or in part because there is no private right of action concerning matters regulated by the Food and Drug Administration under applicable federal laws, regulations, and rules.

72. The warning, labeling, advertising, and sale of the subject pharmaceutical product at issue complied at all times with the FDCA, 21 U.S.C. § 300

et seq. and the Federal Trade Commission Act, 15 U.S.C. § 41 *et seq.* Consequently, Plaintiff's Complaint is preempted by these acts and compliance with these acts constitutes a complete or partial defense to the allegations of Plaintiff's Complaint against Defendant, including any claim for punitive damages. Alternatively, Defendant is entitled to a presumption that the subject pharmaceutical product at issue is not defective or unreasonably dangerous and that it's labeling was adequate.

73. Defendant alleges that the pharmaceutical product at issue was fit and proper for its intended purpose and that the utility of the subject pharmaceutical product at issue outweighs any possible risk inherent in the use of the subject pharmaceutical product.

74. Defendant is informed and believes and thereon alleges that Plaintiff failed to provide Defendant with timely notice of any alleged nonconformance with any express representation.

75. To the extent that Plaintiff seeks punitive damages for the conduct which allegedly caused injuries asserted in the Complaint, punitive damages are barred or reduced by applicable law or statute or, in the alternative, are unconstitutional insofar as they violate the due process protections afforded by the United States Constitution, the excessive fines clause of the Eighth Amendment of the United States Constitution, the Commerce Clause of the United States Constitution, the Full Faith and Credit Clause of the United States Constitution, and applicable provisions of the Constitution of the State of Minnesota. Any law, statute, or other authority

purporting to permit the recovery of punitive damages in this case is unconstitutional, facially and as applied, to the extent that, without limitation, it: (1) lacks constitutionally sufficient standards to guide and restrain the jury's discretion in determining whether to award punitive damages and/or the amount, if any; (2) is void for vagueness in that it failed to provide adequate advance notice as to what conduct will result in punitive damages; (3) permits recovery of punitive damages based on out-of-state conduct, conduct that complied with applicable law, or conduct that was not directed, or did not proximately cause harm, to Plaintiff; (4) permits recovery of punitive damages in an amount that is not both reasonable and proportionate to the amount of harm, if any, to Plaintiff and to the amount of compensatory damages; if any; (5) permits jury consideration of net worth or other financial information relating to this Defendant; (6) lacks constitutionally sufficient standards to be applied by the trial court in post-verdict review of any punitive damages awards; (7) lacks constitutionally sufficient standards for appellate review of punitive damages awards; and (8) otherwise fails to satisfy Supreme Court precedent.

76. Plaintiff's claims are barred because she would have taken the subject pharmaceutical product even if the subject pharmaceutical product's labeling contained the information that Plaintiff contends should have been provided.

77. Plaintiff's claims are barred, in whole or in part, because the advertisements, if any, and labeling with respect to the subject pharmaceutical product were not false or misleading and, therefore, constitute

protected commercial speech under the applicable provisions of the United States Constitution.

78. Defendant made no warranties of any kind, express or implied, or any representations of any nature whatsoever to Plaintiff herein. Additionally, as a manufacturer and not a seller, Defendant is not subject to liability for implied warranties without privity, i.e., proof of direct and specific transactions between the Plaintiff and Defendant. If any such warranties were made, whether express or implied, which Defendant specifically denies, then Plaintiff failed to give timely notice of any breach thereof.

79. Plaintiff's claims against Actavis are barred by Restatement (Second) of Torts Section 402A and the comments thereto, and by the Restatement (Third) of Torts Product Liability §§ 4 and 6, *et. seq.*

80. Neither Plaintiff nor Plaintiff's respective physicians were induced to prescribe or use Reglan® and/or generic metoclopramide based on any material representations or misrepresentations of Actavis.

81. Plaintiff did not rely on any express or implied warranty allegedly made by Actavis.

82. Plaintiff's alleged damages were caused in whole or in part by Plaintiff's failure to mitigate such damages.

83. Plaintiff's causes of action may be barred, in whole or in part, by the doctrines of laches, waiver, and estoppel.

84. Plaintiff's causes of action may be barred, in whole or in part, by the applicable statute of limitations.

85. Plaintiff impermissibly seeks to impose liability on conduct protected from liability by the First Amendment to the United States Constitution.

86. In the absence of proof by Plaintiff that the product used and ingested by Plaintiff was made or distributed by Actavis, Actavis may not be held liable for any claim herein.

87. Actavis expressly reserves the right to assert any additional affirmative defenses that may become apparent through discovery in this case and expressly reserves the right to amend its Answer to assert any such affirmative defenses.

WHEREFORE, Actavis respectfully requests dismissal of Plaintiff's claims and an award of costs, interests, fees and such other and further relief as the Court deems necessary and proper.

TRIAL BY JURY IS HEREBY DEMANDED

Pursuant to Rule 38(b) of the Federal Rules of Civil Procedure, Defendant Actavis-Elizabeth, LLC. hereby restates its demand for a trial by jury, composed of the maximum number of jurors allowed by law, on all of the issues in this case.

Dated: November 13, 2007

s/ Michael D. Hutchens
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IN THE UNITED STATES DISTRICT COURT
District of Minnesota

CASE NO. 07-CV-3919 (DWF/SRN)

[Filed February 22, 2008]

Gladys Mensing,	)
	)
v.	)
	)
WYETH, INC. (d/b/a WYETH); SCHWARZ PHARMA, INC.; PLIVA, INC.; TEVA PHARMACEUTICALS, USA, INC.; ALPHARMA, INC., d/b/a ALPHARMA PHARMACEUTICALS; UDL LABORATORIES, INC.; ACTAVIS ELIZABETH, LLC, and PUREPAC PHARMACEUTICAL CO., and the following fictitious party defendants (whether singular or plural, individual or corporate): No. 1, that entity which originally obtained permission from the U.S. Food and Drug Administration to market the drug branded Reglan; No. 2, that entity which obtained permission from the FDA to market the Reglan, metoclopramide and/or metoclopramide HCl ingested by Gladys Mensing; No. 3, that entity which originally manufactured and sold any Reglan which was ultimately ingested by Gladys Mensing; No. 4, that entity which originally manufactured and sold any Reglan, metoclopramide and/or metoclopramide HCl which was ultimately ingested by Gladys Mensing; No. 5, that entity which marketed Reglan or generic metoclopramide and/or	)

metoclopramide HCl, jointly and individually,)
)
Defendants.)
)

FIRST AMENDED COMPLAINT AND DEMAND FOR JURY TRIAL

Gladys Mensing, Plaintiff, by and through her undersigned attorneys, states and alleges as follows:

I. PARTIES

1. Gladys Mensing, Plaintiff, (hereinafter referred to as "Plaintiff") is an individual of the full age of majority who is a resident and citizen of Steele County, Minnesota.

2. Plaintiff brings this action for the purpose of recovering all damages allowable by law for personal injuries she suffered as a result of ingesting Reglan, metoclopramide and/or metoclopramide HCl (hereinafter "Reglan/ metoclopramide").

3. Defendant, Wyeth, Inc., d/b/a Wyeth (hereinafter "Wyeth") is a Delaware corporation with its principal place of business at 5 Giralda Farms, Madison, New Jersey 07940.

4. References in this Complaint to "Wyeth" include individually and collectively all divisions and/or subsidiaries, Wyeth as successor in interest to A.H. Robins, Inc., American Home Drugs Corporation, and ESI, Lederle, Inc.

5. At all times material hereto, Wyeth was engaged in the business of testing, developing, manufacturing, labeling, marketing, distributing, promoting and/or selling, either directly or indirectly, through third parties, as successor in interest, or other related entities, Reglan/metoclopramide in the State of Minnesota and in interstate commerce. Wyeth may be served with process through its registered agent, Corporation Service Company, 2711 Centerville Road, Suite 400, Wilmington, DE 19808. Wyeth is subject to the jurisdiction and venue of this Court.

6. Wyeth manufactures and distributes generic metoclopramide through its ownership of ESI Lederle, Inc. (hereinafter "ESI"), a former subsidiary which merged into Wyeth.

7. Defendant, Schwarz Pharma, Inc., (hereinafter "Schwarz") is a Delaware corporation, duly qualified to do business in the State of Minnesota with its principal place of business in Mequon, Wisconsin.

8. Defendant Schwarz, one of its predecessors in interest, and/or one of its family of wholly owned divisions was engaged in the business of testing, developing, manufacturing, labeling, marketing, distributing, promoting and/or selling, either directly or indirectly, through third parties, as successor in interest, or other related entities, Reglan/metoclopramide in the State of Minnesota and in interstate commerce. Schwarz may be served with process through its registered agent, CSC Entity Services, LLC, 103

Foulk Road, Suite 200, Wilmington, Delaware 19803. Schwarz Pharma, Inc. is subject to the jurisdiction and venue of this Court.

9. The Defendant, Pliva USA, Inc., (hereinafter "Pliva") is a New York corporation with its principal place of business in New Jersey.

10. At all times material hereto, Pliva was engaged in the business of testing, developing, manufacturing, labeling, marketing, distributing, promoting and/or selling, either directly or indirectly, through third parties or related entities, Reglan/metoclopramide in the State of Minnesota and in interstate commerce. Pliva may be served with process through its agent for service of process at Corporation Trust Company, 820 Bear Tavern Road, 3rd Floor, West Trenton, NJ 08628. Pliva is subject to the jurisdiction and venue of this Court.

11. The Defendant, Teva Pharmaceuticals, USA, Inc., (hereinafter "Teva") is a Delaware corporation with its principal place of business in Pennsylvania.

12. At all times material hereto, Teva was engaged in the business of testing, developing, manufacturing, labeling, marketing, distributing, promoting and/or selling, either directly or indirectly, through third parties or related entities, Reglan/metoclopramide in the State of Minnesota and in interstate commerce. Teva may be served with process through its registered agent, the Corporation Trust Company, located at Corporation Trust Center,

1209 Orange Street, Wilmington, DE 19801. Teva is subject to the jurisdiction and venue of this Court.

13. The Defendant, Alpharma Inc., d/b/a Alpharma Pharmaceuticals (hereinafter "Alpharma"), is a Delaware Corporation and is the parent corporation of Purepac Pharmaceutical Co., which at all times pertinent hereto manufactured and distributed the generic drug Reglan/metoclopramide.

14. At all times material hereto, Alpharma was engaged in the business of testing, developing, manufacturing, labeling, marketing, distributing, promoting and/or selling, either directly or indirectly, through third parties or related entities, Reglan/metoclopramide in the State of Minnesota and in interstate commerce. Alpharma is subject to the jurisdiction and venue of this Court. Alpharma may be served with process through its agent for service: Corporation Service Company, 2711 Centerville Road, Suite 400, Wilmington, Delaware 19809.

15. The Defendant, Purepac Pharmaceutical Co. (hereinafter "Purepac"), is a New Jersey Corporation.

16. At all times material hereto, Purepac was engaged in the business of testing, developing, manufacturing, labeling, marketing, distributing, promoting and/or selling, either directly or indirectly, through third parties or related entities, Reglan/metoclopramide in the State of Minnesota and in interstate commerce.

Purepac may be served with process through its corporate headquarters, 1 Executive Drive, Fort Lee, New Jersey 07024-3309. Purepac is subject to the jurisdiction and venue of this Court.

17. The Defendant, UDL Laboratories, Inc., (hereinafter "UDL Labs") is an Illinois Corporation.

18. At all times material hereto, UDL Labs was engaged in the business of testing, developing, manufacturing, labeling, marketing, distributing, promoting and/or selling, either directly or indirectly, through third parties or related entities, Reglan/metoclopramide in the State of Minnesota and in interstate commerce. UDL Labs may be served with process through its agent for process: Illinois Corporation Service, 801 ADLAI Stevenson Drive, Springfield, Illinois 62703. UDL Labs is subject to the jurisdiction and venue of this Court.

19. The Defendant, Actavis Elizabeth, LLC, (hereinafter "Actavis"), is a New Jersey Corporation.

20. At all times material hereto, Actavis was engaged in the business of testing, developing, manufacturing, labeling, marketing, distributing, promoting and/or selling, either directly or indirectly, through third parties or related entities, Reglan/metoclopramide in the State of Minnesota and in interstate commerce. Actavis is subject to the jurisdiction and venue of this Court.

21. Fictitious parties No. 1 through 6 are party Defendants the identities of whom or which is otherwise unknown to Plaintiff at this time, but, whose true names will be substituted by amendment when the aforesaid lacking knowledge is ascertained.

22. All Defendants, identified *supra*, inclusive, and each of them, may be referred to in this complaint collectively as "DEFENDANTS."

23. At all relevant times, DEFENDANTS were acting by and through their agents, servants and/or employees, each of whom were acting within the scope and course of their employment by agency or authority on their behalf.

24. At all times relevant hereto, DEFENDANTS were in the business of researching, designing, formulating, compounding, testing, manufacturing, producing, processing, assembling, inspecting, distributing, marketing, labeling, promoting, packaging and/or advertising the pharmaceutical drugs known as Reglan/metoclopramide in the State of Minnesota and in interstate commerce.

II. VENUE AND JURISDICTION

25. The venue and jurisdiction of this action is proper because DEFENDANTS conducted business in the State of Minnesota through pharmaceutical sales representatives in the State of Minnesota and because DEFENDANTS were engaged in testing, developing, manufacturing, labeling, marketing,

distributing, promoting and/or selling, either directly or indirectly, through third parties or related entities Reglan/ metoclopramide; thus, there exists a sufficient nexus between the DEFENDANTS' forum contacts and Plaintiff's claims to justify this venue and the assertion of jurisdiction in Minnesota.

III. FACTUAL BACKGROUND OF PLAINTIFF'S CLAIMS

26. During all material times, Plaintiff Gladys Mensing was domiciled in the State of Minnesota.

27. On or about March 23, 2001, Plaintiff's physician prescribed Reglan at a dosage of 5 mg, b.i.d., to treat Plaintiff's diabetic gastroparesis.

28. The active ingredient, metoclopramide and metoclopramide HCl, is a dopamine antagonist.

29. Subsequently, Plaintiff's physician increased Plaintiff's dosage to 10 mg to be taken four (4) times a day.

30. Subsequently, Plaintiff's physician increased the dosage of Plaintiff's prescription for Reglan/metoclopramide and prescribed it to Plaintiff for several years thereafter.

31. Upon information and belief, in prescribing the Reglan/metoclopramide to Plaintiff on a long-term basis, Plaintiff's physicians relied upon information published in the package inserts and/or the Physician's Desk Reference

(hereinafter "PDR") or otherwise disseminated by the Reference Listed Drug Company (hereinafter "RLD") and/or the New Drug Application Holder (hereinafter "NDA holder").

32. Plaintiff ingested Reglan/metoclopramide as prescribed.

33. Plaintiff used the pharmaceutical drugs Reglan/metoclopramide without substantial change in condition of the drugs between the time of design and manufacture of the drugs and the time Plaintiff used the drugs as directed.

34. Plaintiff's long term ingestion of Reglan/metoclopramide caused her injuries.

35. Plaintiff's physicians were not aware of information different from or contrary to the inaccurate, misleading, materially incomplete, false and/or otherwise inadequate information disseminated in the PDR, RLD, or by the NDA holders.

36. On or about March of 2005, Plaintiff was taken to Plaintiff's physician, who discontinued Plaintiff's Reglan/metoclopramide prescription due to the clinical presentation of lip smacking and tongue thrusting movements.

37. On or about September of 2005, Plaintiff was examined by Dr. Bruce A. Evans, Department of Neurology, Mayo Clinic, who diagnosed her as suffering from drug induced Tardive Dyskinesia

related to her long-term use of Reglan/ metoclopramide.

38. Plaintiff's use of Reglan/metoclopramide, as prescribed, resulted in overexposure to the drugs which caused Plaintiff to suffer serious, permanent and disabling injuries, including but not limited to injuries of or associated with the central nervous and extrapyramidal motor systems, including Tardive Dyskinesia, a severe and often permanent disfiguring neurological movement disorder.

39. Plaintiff's serious and permanent injuries, as described above, came about as a foreseeable and proximate result of the DEFENDANTS' dissemination of inaccurate, misleading, materially incomplete, false, and otherwise inadequate information concerning the potential effects of exposure to and long term ingestion of Reglan/metoclopramide to the medical community, physicians, Plaintiff's physician, Plaintiff and other foreseeable users of the drug.

40. Plaintiff has experienced and will continue to experience medical and related expenses, loss of ability to provide household services, disfigurement, disability, pain and suffering, psychological injury and other injuries and damages due to the injuries she suffered caused by the ingestion of this drug.

IV. ALLEGATIONS

41. This case involves DEFENDANTS' failure to warn doctors and patients of information within

its knowledge or possession or both, which indicated the subject Reglan/metoclopramide, when taken for an extended period of time, caused serious, permanent, and debilitating side effects, including tardive dyskinesia.

42. DEFENDANTS jointly and severally, marketed, manufactured and distributed Reglan/metoclopramide and encouraged the long term use of these drugs, misrepresented the effectiveness of these drugs and concealed the drug's dangerous side effects.

Reglan/Metoclopramide: Indications and Resulting Side Effects

43. Reglan/metoclopramide is indicated as short-term therapy for symptomatic gastroesophageal reflux and acute and recurrent diabetic gastric stasis.

44. Reglan/metoclopramide is indicated for use for no greater than twelve weeks; however, DEFENDANTS represented that Reglan/metoclopramide was safe for use to treat nausea and or esophageal reflux for durations that exceeded twelve weeks.

45. Patients who use metoclopramide for an extended period of time are at a significantly increased risk of developing a severe and permanent neurological movement disorder.

46. Other serious side effects caused by ingesting Reglan/metoclopramide for an extended period of time include, but are not limited to, central

nervous system disorders, depression with suicidal ideation, akathesia, tardive dyskinesia, tardive dystonia, visual disturbances and interference with drug metabolism.

47. Patients who use Reglan/metoclopramide for long periods of time that are not able to effectively metabolize it are at a greater risk of developing these serious and permanent injuries.

48. In addition, diabetic patients, like Plaintiff, who use metoclopramide for long periods of time are at an even greater risk of developing extrapyramidal side effects than non-diabetic users.

49. Tardive dyskinesia, one of the serious side effect associated with the ingestion of Reglan/ metaclopramide, is a debilitating neurological disorder that often results in involuntary and uncontrollable movements of the head, neck, face, arms, legs and trunk in addition to grotesque facial grimacing and open-mouthed, uncontrollable tongue movements, tongue thrusting, tongue chewing, and other involuntary movements.

50. There is no cure for tardive dyskinesia.

51. Plaintiff's diagnosed tardive dyskinesia, caused by the ingestion of metaclopramide, is permanent.

Defendant Wyeth as Successor in Interest to Reglan's Innovator

52. Wyeth is the successor in interest to A.H. Robins Company, Inc., a Virginia corporation which first obtained approval by the United States Food and Drug Administration (hereinafter "FDA") to distribute metoclopramide, under the brand name "Reglan" under the FDA's New Drug Application (NDA)[1] schema in 1983.

53. Defendant Wyeth's predecessor in interest, A.H. Robins Company, Inc. expressly warranted to some physicians that Reglan/metoclopramide is safe in long-term use.

54. A.H. Robins knew that is its warranties regarding safety for long term use would be relied upon by ordinary, reasonable and prudent physicians who would share that information with other physicians in their community and that eventually physicians would come to rely on A.H. Robins' express warranties about Reglan/metoclopramide's safety in long-term use.

55. A.H. Robins' express warranties about the safety of Reglan/metoclopramide in long-term use were false and intentionally and negligently misleading.

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[1] Upon information and belief, Plaintiff believes Wyeth to be the holder of multiple NDAs' for Reglan, metoclopramide and metoclopramide HCl.

56. As successor in interest to A.H. Robins Company, Inc., Wyeth is legally responsible for the conduct, fraudulent and negligent acts, intentional and willful omissions, and misleading representations and warranties made by A.H. Robins Company, Inc. concerning the safety and adequacy of Reglan/metoclopramide, and all liabilities stemming therefrom.

57. Wyeth manufactured, marketed and distributed Reglan, metoclopramide, and/or metoclopramide HCl through its Wyeth-Ayerst Laboratories Division in St. Davids, Pennsylvania and through its ownership of "ESI".[2]

58. Wyeth knew that it must fully disclose material safety data and information regarding a new drug's chemistry, proposed manufacturing process, proposed model labeling, including warnings about risks and side effects, and test results involving animal studies, clinical studies, and the drug's bioavailability.

59. Wyeth knew that the data and information would be relied upon by the medical community, physicians, Plaintiff's physician, Plaintiff and other like foreseeable users of Reglan/metoclopramide once the NDA was approved and Wyeth was listed as the Reference Listed Drug Company for the drug.

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[2] Upon information and belief, ESI was a former subsidiary which merged into Wyeth on or about December 15, 1998.

60. Wyeth intentionally and negligently disseminated misleading information to physicians' across the country, through a publication known as the *Physicians' Desk Reference* and through aggressive oral marketing plans, about the risks of long term ingestion of Reglan/metoclopramide and the increased risk of extrapyramidal side effects, including tardive dyskinesia, that patients were exposed to.

Defendant Schwarz Knowingly Acquired Metoclopramide's Risks

61. Defendant Schwarz purchased from Wyeth the rights and *liabilities* associated with Reglan/ metoclopramide, the terms of which, upon information and belief, obligated Schwarz to be responsible for claims related to the ingestion or use of Reglan/metoclopramide.

62. Defendant Schwarz entered into an indemnification agreement with Wyeth over the purchase of the innovator, Wyeth's, Reglan, which included disclosure of clinical studies on Reglan/metoclopramide that were not publicly available.[3]

63. Because Defendant Schwarz acquired Defendant Wyeth's Reglan/metoclopramide assets and liabilities while Wyeth was involved

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[3] Plaintiff does not have information regarding the maximum amount of liability under the defendants' indemnification agreement.

in ongoing litigation regarding Reglan/ metoclopramide, and nevertheless agreed to indemnify Wyeth against all claims related to the ingestion of the drug, Schwarz knew or should have known that the NDA label for Reglan/metoclopramide (Wyeth's label) misrepresented the safety of the drug, withheld warnings of the known side effects of the drug, and knew or should have known of the safety issues surrounding it.

Defendants Wyeth & Schwarz's Failed to Act as Required by the FDA

64. Under the FDA schema, Wyeth was and is the Reference Listed Drug Company (RLD), under a specific NDA, for Reglan/metoclopramide.

65. Under the FDA schema, Defendant Schwarz was and remains the RLD and/or NDA holder for Reglan/ metoclopramide.

66. At all times material hereto, Defendants Wyeth and Schwarz, as the NDA holder and/or RLD company, were aware of the serious side effects caused by Reglan/metoclopramide including, but not limited to, central nervous system disorders, depression with suicidal ideation, akathesia, tardive dyskinesia, tardive dystonia, visual disturbances and interference with drug metabolism.

67. Defendants Wyeth and Schwarz had a duty to ensure their warnings to the medical community are accurate and adequate, to conduct safety surveillance of adverse events for

the drug, and to report *any* data related to the safety and/or accuracy of the warnings and information disseminated regarding the drug.

68. Defendants Wyeth and Schwarz represented that Reglan/metoclopramide was safe for use to treat gastritis/gastroesophageal reflux knowing that the drug was not safe for that purpose and was dangerous to the health and body of Plaintiff.

69. Defendants Wyeth and Schwarz represented that Reglan/metoclopramide caused minimal side effects of knowing that the drug causes central nervous system side effects, and extrapyramidal symptoms, among other side effects, far more frequently than represented.

70. Defendants Wyeth and Schwarz had actual knowledge, through their own studies and studies by independent investigators, that doctors frequently prescribed Reglan/ metoclopramide for long term use that was not safe for patients.

71. Defendants Wyeth and Schwarz had actual knowledge, through their own studies and studies by independent investigators, that nearly one-third of all patients who used Reglan/metoclopramide received it on doctor's prescriptions for 12 months or longer, rather than 12 weeks or less.

72. Defendants Wyeth and Schwarz also had actual knowledge, through research by independent investigators, that the risk of tardive dyskinesia

and other extrapyramidal side effects of Reglan/metoclopramide in patients who receive the drug for 12 weeks or longer is approximately 100 times greater than disclosed in package inserts for Reglan and the *Physicians Desk Reference* label for Reglan brand metoclopramide.

73. Defendants Wyeth and Schwarz knew, or through the exercise of reasonable care should have known, that many patients who use Reglan/metoclopramide are not able to effectively metabolize it and that as a foreseeable consequence of their inability to effectively metabolize, those patients have a greater risk of developing serious and permanent injuries.

74. Defendants Wyeth & Schwarz had actual knowledge of facts which demonstrated that representations in the Reglan/metoclopramide package insert, the PDR label, and literature they distributed concerning Reglan/metoclopramide to physicians were false and misleading.

75. Defendants Wyeth and Schwarz failed to correct their label and/or disclose that knowledge to the medical community, physicians, plaintiff and other foreseeable users.

76. It is the public policy of the United States and of this state, as reflected in the Hatch-Waxman Act, to encourage the availability of cheaper, generic drug products that are therapeutically equivalent to name brand products and to

encourage the substitution, as appropriate, of such generic products for name brand products in patients' medical therapy.

77. Defendants Wyeth and Schwarz, as prescription drug manufacturers and/or distributors, knew or ought to have realized that so-called "drug product selection laws," enacted in every state, including this state, authorize or require a prescription for a drug identified by product brand name or by generic name to be filled, subject to certain limited exceptions, with a generic drug product that is therapeutically equivalent to the name brand drug product.

78. Defendants Wyeth and Schwarz knew or ought to have realized that generic drug manufacturers, choosing to take advantage of the Hatch-Waxman Act, initially copy verbatim the package insert for the name brand prescription drug product and place that information contained in the package inserts accompanying their own generic prescription drug products to ensure its label is accurate and not misleading and conforms to the innovative drug product.

79. Defendants Wyeth and Schwarz knew or ought to have known that the generic drug manufacturers also typically rely upon the marketing efforts of the name brand manufacturer to generate sales of their own products.

80. Defendants Wyeth and Schwarz knew or ought to have realized that physicians commonly

consult the information disseminated by the name brand manufacturer, in PDR labels or otherwise, and rely upon that information in their decisions concerning the prescribing of those products for their patients.

81. Defendants Wyeth and Schwarz knew or ought to have realized, specifically, that physicians would rely upon information disseminated to them by the name brand manufacturer, regardless of whether the prescriptions might be filled with either the name brand product, Reglan, or generic Reglan/metoclopramide, and that many patients, in accordance with those prescriptions, would be likely to ingest generic Reglan/metoclopramide.

Generic Defendants Failed to Act as Required by the FDA

82. Defendants Pliva, Teva, UDL Labs, Actavis, Purpac, Wyeth by and through ESI, and Fictious Parties 1-6 each submitted an Abbreviated New Drug Application (ANDA) to the U.S. Food and Drug Administration, based on representations made by the RLD Company, requesting permission to manufacture, market, and distribute generic Reglan/metoclopramide. All Defendants, identified in this paragraph above, inclusive, and each of them, may be referred to in this complaint collectively as "GENERIC DEFENDANTS."

83. Under the ANDA process, the Code of Federal Regulations *required* the GENERIC DEFENDANTS to submit a label for Reglan/

metoclopramide, initially identical in all material aspects to the reference listed drug label.

84. Under the Code of Federal Regulations, GENERIC DEFENDANTS had a duty to ensure their Reglan/metoclopramide warnings to the medical community were accurate and adequate, to conduct post market safety surveillance, to review all adverse drug event information (ADE), and to report any information bearing on the risk and/or prevalence of side effects caused by Reglan/metoclopramide.

85. Under the Code of Federal Regulations, if GENERIC DEFENDANTS discover information in the course of the fulfillment of their duties as outlined above, GENERIC DEFENDANTS must report that information to the medical community, Plaintiff's physician, Plaintiff and other foreseeable users of Reglan/ metoclopramide to ensure that their warnings are continually accurate and adequate.

86. GENERIC DEFENDANTS failed to investigate the accuracy of its metoclopramide and/or metoclopramide HCl drug label once it became aware of signals indicating a safety issue.

87. GENERIC DEFENDANTS failed to review the medical literature for the metoclopramide drug and/or metoclopramide HCl drug.

88. GENERIC DEFENDANTS relied upon the name brand manufacturer and the reference

listed drug company to review the aforementioned medical literature for Reglan/metoclopramide.

89. Under the FDA schema, if the FDA approves a label change as requested by an ANDA holder, the NDA holder (also referred to as the Reference Listed Drug Company) must also amend its label.

90. GENERIC DEFENDANTS failed to communicate the true and accurate risks and/or prevalence of severe neurological side effects resulting from the ingestion of drugs containing Reglan/metoclopramide.

DEFENDANTS Failed to Meet Labeling & Package Insert Requirements

91. DEFENDANTS disseminated to physicians, through package inserts, the publication of a PDR label, and otherwise, information concerning the properties and effects of Reglan/metoclopramide, with the intention that physicians would rely upon that information in their decisions concerning the prescription of drug therapy for their patients.

92. DEFENDANTS knew, or should have known through the exercise of reasonable care, that the package insert for Reglan/metoclopramide substantially understated the prevalence of acute and long term side effects of ingesting the drug.

93. DEFENDANTS failed to use reasonable care to modify the package insert to adequately warn physicians about the true risks of both short term use and long term use, even after several injured patients filed lawsuits alleging inadequate warnings and produced competent expert testimony supporting their allegations.

94. DEFENDANTS owed a duty in all of their several undertakings, including the dissemination of information concerning Reglan/metoclopramide, to exercise reasonable care to ensure that they did not create unreasonable risks of personal injury to others.

DEFENDANTS Failed to Disclose Known, Serious Side Effects

95. Reglan/metoclopramide was widely advertised by DEFENDANTS as a safe and effective treatment of diabetic gastroparesis, gastroesophageal reflux disease (GERD) and other gastrointestinal disorders.

96. DEFENDANTS failed to conduct and report post market safety surveillance on Reglan/metoclopramide.

97. DEFENDANTS failed to review all adverse drug event information (ADE)[4] and to report any

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[4] Defendants are required to review all adverse drug experience information obtained or otherwise received ... from any source ... including derived from postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports from

information bearing upon the adequacy and accuracy of their warnings, efficacy, or safety, including the risks and/or prevalence of side effects caused by Reglan/metoclopramide.

98. DEFENDANTS failed to monitor all relevant scientific literature related to Reglan/metoclopramide.

99. DEFENDANTS failed to disclose material safety information regarding the serious and permanent side effects caused by taking Reglan/metoclopramide for long periods of time.

100. DEFENDANTS failed to report data, *regardless of the degree of significance*, regarding the adequacy and/or accuracy of its warnings, efficacy, or safety of Reglan/metoclopramide.

101. DEFENDANTS knowingly concealed from physicians material facts bearing on the interpretation of package insert disclosures that exposure to Reglan/metoclopramide can lead to Tardive Dyskinesia and other EPS, that the risk is "believed" to increase with duration of therapy and total cumulative dose, and that therapy for longer than twelve (12) weeks "cannot be recommended."

102. DEFENDANTS concealed the fact that earlier false information disseminated by A.H. Robins Co., representing long term Reglan/

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the scientific literature, and unpublished scientific reports. 21 C.F.R. § 317.80(b).

metoclopramide therapy to be reasonably safe, was unscientific and false.

103. DEFENDANTS concealed the fact that Reglan/metoclopramide is a neuroleptic agent and dopamine antagonist, which can be expected to lead to Tardive Dyskinesia and other EPS with approximately the same high frequency, particularly in longer term use, as other neuroleptic drugs and that epidemiological studies have consistently confirmed this expectation.

104. DEFENDANTS also concealed the fact that the treatment of chronic or intermittent gastroesophageal reflux and/or diabetic gastroporesis, and/or other gastric disorders with Reglan/metoclopramide products for longer than 12 weeks is unlikely to be reasonably safe.

105. Some or all of the other DEFENDANTS, as a result of their participation as DEFENDANTS in previous litigation concerning Reglan and other Reglan, metoclopramide and/or metoclopramide HCl products, received clear notice of WYETHS suppression of important safety information concerning Reglan, metoclopramide and/or metoclopramide HCl and their products, yet despite this notice chose to ignore the information and join consciously in the suppression.

V. WRONGFUL CONDUCT

COUNT 1
STRICT PRODUCTS LIABILITY

106. Plaintiff repeats, reiterates, and realleges each and every allegation contained in this complaint with the same force and effect as if fully set forth herein.

107. DEFENDANTS developed, marketed and distributed Reglan/ metoclopramide to the general public even after learning of the design, manufacturing, and side effect defects that threatened the foreseeable use of the drug.

108. Reglan/metoclopramide was defective and unreasonably dangerous and was expected to and did reach Plaintiff without substantial change in the drug.

109. DEFENDANTS had prior knowledge and information within there possession that indicated their Reglan/metoclopramide was dangerous and unreasonably capable of causing severe physical, mental and emotional injuries.

110. Despite such knowledge, DEFENDANTS knowingly and deliberately failed to warn the public, including Plaintiff, of the extreme risk of physical injury occasioned by the defects inherent in their Reglan/metoclopramide for the purpose of increasing profits and in order to advance their own pecuniary interests.

111. Reglan/metoclopramide was not reasonably safe as designed because the foreseeable risks involved in its use at the time the product left the possession of the DEFENDANTS clearly outweighed the utility of the product or its therapeutic benefits.

112. DEFENDANTS knew or should have known through testing, adverse event reporting, or otherwise, that the drug created a high risk of bodily injury and serious harm.

113. DEFENDANTS failed to provide timely and adequate warning or instructions regarding Reglan/metoclopramide with known design, manufacturing, and side effect defects.

114. DEFENDANTS failed to provide timely and adequate post-marketing warning or instruction because, after they knew or should have known of the risks of injury from Reglan/metoclopramide associated with long term use as commonly prescribed, they failed to promptly respond to and adequately warn about these risks.

115. DEFENDANTS' Reglan/metoclopramide products are inherently dangerous for their intended use due to design and manufacturing defects and improper warnings of serious side effects, causing injuries and damages to Plaintiff. DEFENDANTS are therefore strictly liable to Plaintiff for damages.

COUNT 2
BREACH OF EXPRESS WARRANTY

116. Plaintiff repeats, reiterates, and realleges each and every allegation contained in this Complaint with the same force and effect as if fully set forth herein.

117. DEFENDANTS' concealment and failure to warn through promotional statements and product literature expressly warranted to Plaintiff that Reglan/metoclopramide was safe and capable of treating gastrointestinal disorders, including diabetic gastroparesis, a long term chronic condition.

118. In response to these promises and express statements, Plaintiff and Plaintiff's physicians relied on such affirmations and warranties to Plaintiff through Plaintiff's physicians.

119. Reglan/metoclopramide does not conform to those express representations in light of recently discovered disclosures and information previously withheld by DEFENDANTS. DEFENDANTS' express warranty through its false statements failed to disclose and provide patient approval of the design, manufacturing and safety defects inherent in the drug.

120. DEFENDANTS breached their warranty of the pharmaceutical soundness of Reglan/ metoclopramide by continuing sales and marketing campaigns highlighting the safety of the drug, while they knew of the design, manufacturing and safety defects and risk of

contracting a severe neurological disorder which was posed by use of the drug.

121. As a direct and proximate result of DEFENDANTS' breach of their express warranty, Plaintiff suffered bodily and mental injury, harm, other compensable injury and economic losses, compensable through this Court.

COUNT 3
BREACH OF IMPLIED WARRANTIES

122. Plaintiff repeats, reiterates, and realleges each and every allegation contained in this Complaint with the same force and effect as if fully set forth herein.

123. DEFENDANTS' concealment and failure to warn impliedly warranted the medical soundness of Reglan/metoclopramide by marketing, promoting, selling, and distributing the drug as achieving merchantable quality and as safe and fit for its intended use. DEFENDANTS further warranted Reglan/ metoclopramide as able to perform and provide treatment of patients with symptomatic gastroesophageal reflux and acute and recurrent diabetic gastric stasis.

124. Plaintiff reasonably relied on the presumption that DEFENDANTS would provide notice, disclosure, or warnings of any risks associated with Reglan/metoclopramide's merchantability, quality, safety, and fitness for its intended use.

125. Contrary to such implied warranties, Reglan/metoclopramide was not of merchantable quality or safe or fit for its intended use, because the drugs were and are unreasonably dangerous and unfit for the ordinary, intended, and foreseeable use due to their adverse side effects.

126. DEFENDANTS knew that most physicians who prescribed Reglan/metoclopramine were not aware the drug is a dopamine antagonist and/or a neuroleptic agent, which is just as likely to cause serious extrapyramidal side effects as other dopamine antagonists and/or other neuroleptic drugs.

127. DEFENDANTS also knew that the risks of potentially irreversible neurological side effects when Reglan/metoclopramide is used long term were much greater than most physicians realized. By failing to give adequate warnings about the dopamine antagonist and/or neuroleptic properties of Reglan/metoclopramide and the risk of long term use that is associated with those properties, the DEFENDANTS breached implied warranties of merchantability and fitness for the ordinary use of Reglan/metoclopramide.

128. As a direct and proximate result of DEFENDANTS' breach of their implied warranties, Plaintiff suffered economic loss and other compensable injuries as alleged herein, and is therefore entitled to compensatory damages and equitable relief according to proof.

COUNT 4
NEGLIGENCE

129. Plaintiff repeats, reiterates, and realleges each and every allegation contained in this Complaint with the same force and effect as if fully set forth herein.

130. DEFENDANTS had a duty to exercise the care of an expert in all aspects of the formulation, manufacture, compounding, testing, inspection, packaging, labeling, distribution, marketing, and sale of Reglan/metoclopramide to insure the safety of its drug and to insure that the consuming public, including the Plaintiff and Plaintiff's physicians and agents, obtained accurate information and instructions for the safe use or non-use of this drug.

131. DEFENDANTS failed to discharge this duty by distributing a defective drug into the stream of commerce without warning or notice of the foreseeable unreasonably dangerous side effects. DEFENDANTS' failure of duty exposed Plaintiff to a high risk of bodily injury and serious harm.

132. DEFENDANTS' breach of their duties proximately caused damages to Plaintiff. As a direct and proximate cause of DEFENDANTS' conduct, Plaintiff has suffered and will continue to suffer injury, harm, and economic loss as alleged herein, including a permanent and substantial physical disability, and expenses attributable to this disability. DEFENDANTS breached their duty with the understanding

customers and physicians would rely upon such actions when choosing DEFENDANTS' drug.

133. The DEFENDANTS were negligent and breached duties owed to Plaintiff with respect to metoclopramide, including, but not limited to, one or more of the following respects:

(a) Despite knowledge of hazards and knowledge that the product was frequently prescribed for long term use, they failed to accompany the product with adequate warnings and instructions regarding the adverse and long lasting side effects associated with the use of metoclopramide and particularly with foreseeable long term use;

(b) They failed to conduct adequate testing;

(c) Despite knowledge of hazards, they failed to conduct adequate post-marketing surveillance to determine the safety of the product;

(d) Despite knowledge of hazards, they failed to adequately warn Plaintiff's physicians or Plaintiff that the use of metoclopramide could result in depression with suicidal ideation, akathesia, akinesia, tardive dyskinesia, tardive dystonia, visual disturbances and interferences with drug metabolism; and

(e) Despite the fact that the DEFENDANTS knew or should have known that

metoclopramide caused unreasonably dangerous side effects, they failed to adequately disclose the known or knowable risks associated with metoclopramide as set forth above; they willfully and deliberately failed to adequately disclose these risks, and in doing so, acted with a conscious disregard of Plaintiff's safety or welfare.

134. In the alternative, DEFENDANTS' acts of omissions and concealment of material facts of the foreseeable unreasonably dangerous side effects were made with the understanding patients and physicians would rely upon such statements when choosing DEFENDANTS' drug. Furthermore, the economic damages and physical harm caused by DEFENDANTS' conduct would not have occurred had DEFENDANTS exercised the high degree of care imposed upon it and Plaintiff therefore also pleads the doctrine of *res ipsa loquitur*.

COUNT 5
MISREPRESENTATION BY OMISSION

135. Plaintiff repeats, reiterates, and realleges each and every allegation contained in this Complaint with the same force and effect as if fully set forth herein.

136. DEFENDANTS misrepresented the soundness and reliability of their drug to physicians and the general public through promotional and marketing campaigns. It misrepresented that Reglan/metoclopramide was safe and effective

when used as instructed, when, in fact, it was dangerous to the health of patients. DEFENDANTS continued these misrepresentations for an extended period of time, without disclosing material information.

137. DEFENDANTS took advantage of the limited opportunity Plaintiff had to discover their strategic and intentional concealment of the design, manufacturing and safety defects in Reglan/metoclopramide.

138. At the time DEFENDANTS promoted the drug at issue as safe and/or effective, they did not have adequate proof upon which to base such representations, and in fact, knew or should have known that Reglan/metoclopramide was dangerous.

139. DEFENDANTS concealed these design, manufacturing, and safety defects from the public by withholding information pertaining to the inherent design, manufacturing and safety defects and high risks of a severe and permanent neurological condition relating to their Reglan/metoclopramide and presenting the drug as sound and reliable.

140. DEFENDANTS' intentional misrepresentations and omissions were made willfully, wantonly or recklessly to the Plaintiff to induce purchase of their drug over other drugs on the market.

141. DEFENDANTS knew or should have known of the high risk Plaintiff would encounter by

unwittingly agreeing to ingest their defective drug.

142. DEFENDANTS failed to exercise reasonable care and competence in obtaining and/or communicating information regarding the safe use of Reglan/metoclopramide and otherwise failed to exercise reasonable care in transmitting information to Plaintiff, Plaintiff's physician, and the general public.

143. DEFENDANTS made these representations in the course of their business as designers, manufacturers, and distributors of the drug at issue despite having no reasonable basis for their assertion that these representations were true and/or without having accurate or sufficient information concerning these representations. DEFENDANTS were aware that, without such information, it could not accurately make these representations.

144. At the time these representations were made, DEFENDANTS intended to induce Plaintiff and/or Plaintiff's physicians to rely upon such representations.

145. Said representations were made with the intent to defraud and deceive Plaintiff and/or Plaintiff's physicians and with the intent to induce Plaintiff and/or Plaintiff's physicians to rely upon the statements and use of Reglan/metoclopramide

146. Plaintiff and/or Plaintiff's physicians, at the time the representations were made, were

unaware of their falsity and believed them to be true. In reasonable reliance thereon by Plaintiff and/or Plaintiff's physicians used Reglan/ metoclopramide, and as a result, Plaintiff has suffered, and will continue to suffer, injury, harm and economic loss alleged herein.

147. As a direct and proximate result of reliance upon DEFENDANTS misrepresentations, Plaintiff has suffered and will continue to suffer injury, harm, and economic loss as alleged herein, including a permanent and substantial physical disability, and expenses attributable to this disability.

COUNT 6
CONSTRUCTIVE FRAUD

148. Plaintiff repeats, reiterates, and realleges each and every allegation contained in this Complaint with the same force and effect as if fully set forth herein.

149. DEFENDANTS, while in possession of unique and pertinent information involving the safety and reliability of Reglan/metoclopramide, presented its drug as sound and failed to warn of the drugs inherent design, safety and manufacturing defects. DEFENDANTS suppressed this information and continued sales and marketing of their drug to the general public. DEFENDANTS knew or should have known Plaintiff had no means, other than DEFENDANTS full, accurate, and objective disclosure, of obtaining the relevant information.

150. Through its unique knowledge and expertise regarding the affected nature of Reglan/metoclopramide and through its statements to physicians and their patients in advertisement, promotional materials, and other communications, DEFENDANTS professed and affirmed to Plaintiff its knowledge of the truth of the representation that the drug at issue was safe for its intended use and was free from design, safety and manufacturing defects.

151. DEFENDANTS misrepresentations and omissions were made intentionally to induce Plaintiff to purchase DEFENDANTS' drug in order to reap high profit margins.

152. DEFENDANTS' conduct took unconscionable advantage of its dominant position of knowledge, engaging in constructive fraud in its relationship with Plaintiff. Misled by this veil of fraud, Plaintiff reasonably relied on DEFENDANTS' representations.

153. As a result, Plaintiff has suffered and will continue to suffer injury, harm, and economic loss as alleged herein, including a permanent and substantial physical disability, and expenses attributable to this disability.

COUNT 7
VIOLATION OF THE MINNESOTA DECEPTIVE TRACE PRACTICE ACT

154. Plaintiff repeats, reiterates, and realleges each and every allegation contained in this

Complaint with the same force and effect as if fully set forth herein.

155. DEFENDANTS applied advertising and marketing campaigns representing its Reglan/ metoclopramide as phamalogically sound and medically safe, while DEFENDANTS knew of the drugs' design and manufacturing defects.

156. DEFENDANTS knew of the design and manufacturing defect within Reglan/ metoclopramide, but denied public access to the information, avoiding corporate responsibility. DEFENDANTS knew its patients held a disadvantage in accessing information involving the safety of its affected drugs.

157. DEFENDANTS concealed the design and manufacturing defects of its drugs for the purposes of higher profits and increased sales in its highly profitable heart device division.

158. DEFENDANTS have violated Minn. Stat. § 325D.44(5) by representing its Reglan/ metoclopramide as having characteristics, uses, and benefits of a safe and mechanically sound drug while knowing the statements were false and the drugs contained inherent design and manufacturing defects.

159. DEFENDANTS have violated Minn. Stat. § 325D.44(7) by representing its Reglan/ metoclopramide as a non-defective medical product of a particular standard, quality, or grade while knowing the statements were false

and the drugs contained inherent design and manufacturing defects.

160. DEFENDANTS have violated Minn. Stat. § 325D.44(9) by advertising, marketing, and selling its Reglan/metoclopramide as medically reliable and without a known design and manufacturing defect while knowing those claims were false and without any medical support.

161. DEFENDANTS have violated Minn. Stat. § 325D.44(13) by creating a likelihood of confusion about the efficacy and mechanical soundness of Reglan/metoclopramide, comparing its defective drug with other non-defective products.

162. The Minnesota statutes prohibiting unfair and deceptive trade practices may apply to all transactions with DEFENDANTS because DEFENDANTS' deceptive scheme was carried out in Minnesota and affected all persons who were ingecting Reglan/metoclopramide containing the known defects.

163. Plaintiff seeks to have this practice enjoined and declared unlawful, and is entitled to recover costs, expenses, and attorneys' fees in seeking injunctive and declaratory relief. Minn. Stat. § 325D.45.

COUNT 8
VIOLATION OF THE MINNESOTA FALSE STATEMENT IN ADVERTISING ACT

164. Plaintiff repeats, reiterates, and realleges each and every allegation contained in this Complaint with the same force and effect as if fully set forth herein.

165. DEFENDANTS produced and published advertisements and deceptive and misleading statements of the soundness and mechanical reliability of Reglan/metoclopramide after learning of its inherent design and manufacturing defect, with the intent to sell Reglan/metoclopramide.

166. DEFENDANTS concealed its deceptive practices in order to increase the sale of and profit from Reglan/metoclopramide.

167. DEFENDANTS have violated Minn. Stat. § 325F.67 by intending to sell and create a customer demand for Reglan/metoclopramide using deceptive or untrue statements of fact about the drug's mechanical soundness and reliability on DEFENDANTS' website and medical brochures distributed to patients and physicians.

168. The Minnesota statutes prohibiting false statements in advertising apply to all persons with DEFENDANTS devices because DEFENDANTS' deceptive scheme was carried out in Minnesota and affected all persons ingesting Reglan/metoclopramide.

169. As a result of DEFENDANTS' practices, Plaintiff suffered actual damages. Plaintiff is entitled to recover those damages along with costs, expenses, and attorneys' fees. Minn. Stat. 8.31, subd. 3a.

COUNT 9
VIOLATION OF THE MINNESOTA PREVENTION OF CONSUMER FRAUD ACT

170. Plaintiff repeats, reiterates, and realleges each and every allegation contained in this Complaint with the same force and effect as if fully set forth herein.

171. DEFENDANTS intentionally concealed its design and manufacturing defect in Reglan/metoclopramide and failed to disclose for the purposes of continuing the sale and distribution of its affected drug.

172. DEFENDANTS represented Reglan/metoclopramide was safe and effective and intended that patients and physicians rely on those representations when deciding if DEFENDANTS' drug was optimal for meeting the patient's needs.

173. Through these misleading and deceptive statements and false promises, DEFENDANTS violated Minn. Stat. § 325F.69.

174. The Minnesota statutes prohibiting consumer fraud apply to all persons ingesting DEFENDANTS drug because DEFENDANTS' deceptive scheme was carried out in Minnesota

and affected all persons ingesting Reglan/metoclopramide containing a defect.

175. As a result of DEFENDANTS' practices, Plaintiff suffered actual economic damages and is entitled to recovery of those damages along with attorneys' fees. Minn. Stat. § 8.31, subd. 3a.

COUNT 10
INTENTIONAL INFLICTION OF EMOTIONAL DISTRESS

176. Plaintiff repeats, reiterates, and realleges each and every allegation contained in this Complaint with the same force and effect as if fully set forth herein.

177. Through intentional, reckless, and extreme conduct, DEFENDANTS knowingly denied Plaintiff adequate opportunity in measuring the level of risk related to DEFENDANTS' Reglan/metoclopramide. By withholding information of known design and manufacturing defects and concealing those fatal problems, DEFENDANTS created a false sense of security for Plaintiff, who assumed reasonable safety with DEFENDANTS' drug.

178. DEFENDANTS conduct of intentional omission, concealment, and failure to warn of the design and manufacturing defects caused Plaintiff to suffer injury, harm, and economic loss as alleged herein, including a permanent and substantial physical disability, and expenses attributable to this disability.

179. The injuries described above entitle Plaintiff to compensatory damages and equitable and declaratory relief, along with all appropriate damages according to proof.

COUNT 11
NEGLIGENT INFLICTION OF EMOTIONAL DISTRESS

180. Plaintiff repeats, reiterates, and realleges each and every allegation contained in this Complaint with the same force and effect as if fully set forth herein.

181. DEFENDANTS intentionally and willfully failed to disclose or warn of the inherent risks and defects to its physicians and patients. DEFENDANTS enforced its negligent conduct through manufacturing, marketing, and selling its defective drug to Plaintiff, while knowingly concealing design, manufacturing and safety defects, and misrepresenting the risks of severe side effects, quality, safety, and efficacy of the drug.

182. DEFENDANTS' willful conduct inflicted Plaintiff with severe emotional distress through Plaintiff's subsequent illness, and permanent disability resulting from Reglan/ metoclopramide.

183. DEFENDANTS conduct of willful omission and concealment of design, manufacturing and safety defects in order to induce ingestion of the drug caused Plaintiff severe emotional distress.

184. As a direct result of DEFENDANTS' careless and negligent conduct, Plaintiff has suffered and will continue to suffer injury, harm, and economic loss as alleged herein, including a permanent and substantial physical disability, and expenses attributable to this disability.

COUNT 12
NEGLIGENT MISREPRESENTATION

185. Plaintiff repeats, reiterates, and realleges each and every allegation contained in this Complaint with the same force and effect as if fully set forth herein.

186. DEFENDANTS had actual knowledge of facts which demonstrated that representations in the Reglan.metoclopramide package insert, the PDR label, and literature they distributed to physicians were false and misleading.

187. DEFENDANTS had a reasonable duty of care to disclose the true facts regarding the safety of Reglan to physicians and their patients, pharmacists, and the generic metoclopramide industry.

188. Furthermore, DEFENDANTS had a duty to ensure that they had a reasonable basis for making the representations described above, to exercise reasonable care in making those representations, to accurately make those representations, and to not make misrepresentations.

189. DEFENDANTS breached that duty by failing to disclose important safety information regarding metoclopramide's risks and misrepresenting Reglan/metoclopramide's safety in literature distributed on the drug.

190. DEFENDANTS made such misrepresentations knowing that the Reglan/metoclopramide user reasonably relied on the accuracy of that information, that they would take action based upon it, that individuals would be put in peril by such action, and that those individuals would suffer physical harm as a result.

191. DEFENDANTS' breach of its duties proximately caused damages to Plaintiff. As a direct and proximate cause of DEFENDANTS' conduct, Plaintiff has suffered or will continue to suffer injury, harm, and economic loss as alleged herein, including a permanent and substantial physical disability, and expenses attributable to this disability. DEFENDANTS breached their duty with the understanding patients and physicians would rely upon such actions when choosing DEFENDANTS' drugs.

COUNT 13
FRAUD BY CONCEALMENT

192. Plaintiff repeats, reiterates, and realleges each and every allegation contained in this Complaint with the same force and effect as if fully set forth herein.

193. DEFENDANTS knowingly concealed from physicians serious and permanent side effects

caused by taking Reglan/metoclopramide for long periods of time.

194. DEFENDANTS' misrepresentations and omissions were made intentionally to induce Plaintiff to purchase DEFENDANTS' drug in order to reap the high profit margin relating to DEFENDANTS.

195. Plaintiff's physician, in reliance upon the information disseminated by the DEFENDANTS, and without knowledge of the undisclosed and knowingly concealed facts, determined that the benefits of prolonged Reglan/metoclopramide therapy outweighed the risks for their patients and prescribed a prolonged course of therapy for Plaintiff with Reglan/metoclopramide products.

196. DEFENDANTS' conduct took unconscionable advantage of its dominant position of knowledge, engaging in fraud by concealment in its relationship with Plaintiff. Misled by this veil of fraud, Plaintiff reasonably relied on DEFENDANTS' representations.

197. As a result, Plaintiff has suffered and will continue to suffer injury, harm, and economic loss as alleged herein, including a permanent and substantial physical disability, and expenses attributable to this disability.

COUNT 14
JOINT AND SEVERAL LIABILITY

198. Plaintiff repeats, reiterates, and realleges each and every allegation contained in this Complaint with the same force and effect as if fully set forth herein.

199. By virtue of their individual and collective acts and omissions, Defendants are jointly and severally liable to Plaintiff as such acts and omissions have proximately caused Plaintiff to suffer a single indivisible injury for which each Defendant is responsible.

VI. DAMAGES

200. As a direct and proximate result of the acts and omissions of the DEFENDANTS, Plaintiff ingested Reglan, which was causally related to and contributed to Plaintiff's development of the permanent neurological disorder known as Tardive Dyskinesia.

201. As a direct and proximate result of the acts and omissions of the Defendants, Plaintiff has suffered extreme emotional distress, anguish, physical and mental suffering, loss of the ability to control Plaintiff's facial expressions, mouth, tongue and jaw, which has rendered Plaintiff's physically incapacitated.

202. As a direct and proximate result of the acts and omissions of the Defendants, Plaintiff experiences extreme embarrassment, shame,

anguish, anxiety, and has a sustained a loss of enjoyment of life.

203. Plaintiff seeks the recovery for past and future special damages, which includes medication, doctor, rehabilitation, therapy, and other assisted living and nursing care and Plaintiff also seeks general damages in the amount to be determined for the wrongful conduct of each of the DEFENDANTS, jointly and individually.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff prays for relief against Defendants as follows:

1. For judgment for damages sufficient to compensate for damages in excess of $75,000.00, including but not limited to past, present, and future economic expenditures in connection with DEFENDANTS' Reglan/metoclopramide;

2. For compensatory damages according to proof;

3. For all applicable statutory remedies that assert liability for DEFENDANTS' wrongdoings and improper conduct;

4. For a disgorgement of profits;

5. For prejudgment interest, as permitted by law;

6. For reasonable costs, including attorneys fees as permitted by law; and

7. For all other just and proper relief.

Plaintiff seeks a trial by jury on all issues.

Date: February 22, 2008

Respectfully Submitted,

GOLDENBERG & JOHNSON, PLLC

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UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MINNESOTA

CASE NO.: 07-CV-3919 PJS/RLE

[Filed March 11, 2008]

GLADYS MENSING,

Plaintiff,

vs.

WYETH, INC. (d/b/a WYETH), SCHWARZ PHARMA, INC.; PLIVA, INC.; TEVA PHARMACEUTICALS, USA, INC.; ALPHARMA, INC., d/b/a ALPHARMA PHARMACEUTICALS; UDL LABORATORIES, INC.; ACTAVIS ELIZABETH LLC; and PUREPAC PHARMACEUTICAL CO., and the following fictitious party defendants (whether singular or plural, individual or corporate): No. 1, that entity which originally obtained permission from the U.S. Food and Drug Administration to market the drug branded Reglan; No. 2 that entity which obtained permission from the FDA to market the Reglan, metoclopramide and/or metoclopramide HCl ingested by Gladys Mensing; No. 3, that entity which originally manufactured and sold any Reglan which was ultimately ingested by Gladys Mensing; No. 4, that entity which originally manufactured and sold any Reglan, metoclopramide and/or metoclopramide HC1 which was ultimately ingested by Gladys

Mensing; No. 5, that entity which marketed Reglan or generic metoclopramide and/or metoclopramide HCl,

Defendants.

DEFENDANT ACTAVIS ELIZABETH LLC'S ANSWER TO PLAINTIFF'S AMENDED COMPLAINT

JURY TRIAL DEMANDED

Defendant Actavis Elizabeth LLC (hereinafter Actavis or Defendant), by and through counsel and for its Answer to Plaintiff Gladys Mensing's Amended Complaint, states as follows:

PARTIES

1. Actavis is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraphs 1, 2, and 3 of Plaintiff's Amended Complaint. Therefore, Actavis denies the allegations in those paragraphs.

2. The allegations in paragraph 4 of Plaintiff's Amended Complaint are definitional statements relating to other Defendants to which no response is necessary by this Defendant but to the extent that this paragraph alleges claims against this answering Defendant, such allegations are denied.

3. Actavis is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraphs 5 through 12 of Plaintiff's

Amended Complaint. Therefore, Actavis denies the allegations in paragraphs 5 through 12 of Plaintiff's Amended Complaint.

4. In response to paragraph 13 of Plaintiff's Amended Complaint, Actavis denies that Purepac Pharmaceutical Co. is still in existence and answering further states that at one time when Purepac Pharmaceutical Co. was in existence Alpharma Inc. was the parent corporation. Actavis admits that Alpharma Inc. was and is a Delaware Corporation. Answering further, Defendant admits that Purepac Pharmaceutical Co. did manufacture and distribute metoclopramide but denies all remaining allegations of paragraph 13 of Plaintiff's Amended Complaint.

5. Actavis denies the allegations in paragraphs 14 through 15 of Plaintiff's Amended Complaint.

6. In response to the allegations contained in paragraph 16 of Plaintiff's Amended Complaint, Actavis admits that when Purepac Pharmaceutical Co. was in existence it did manufacture and distribute metoclopramide but denies all the remaining allegations in paragraph 16 of Plaintiff's Amended Complaint.

7. Actavis is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 17 through 18 of Plaintiff's Amended Complaint. Therefore, Actavis denies the allegations in paragraph 17 through 18 of Plaintiff's Amended Complaint.

8. Actavis denies the allegations contained in paragraph 19 of Plaintiff's Amended Complaint.

9. In response to paragraph 20 of Plaintiff's Amended Complaint, Actavis admits that it manufactures and distributes metoclopramide and denies all the remaining allegations in paragraph 20 of Plaintiff's Amended Complaint.

10. Actavis is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 21 of Plaintiff's Amended Complaint. Therefore, Actavis denies the allegations in paragraph 21 of Plaintiff's Amended Complaint.

11. The allegations in paragraph 22 of Plaintiff's Amended Complaint are definitional statements to which no response is necessary by this Defendant but to the extent that this paragraph alleges claims against this answering Defendant, such allegations are denied.

12. In response to paragraphs 23 through 24 of Plaintiff's Amended Complaint, Actavis admits that it currently manufactures and distributes metoclopramide and that Purepac Pharmaceutical Co. previously did so but denies the remaining allegations contained in these paragraphs.

VENUE AND JURISDICTION

13. Actavis is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 25 of Plaintiff's Amended Complaint as it relates to the other Defendants and denies the allegations as to itself.

FACTUAL BACKGROUND OF PLAINTIFF'S CLAIMS

14. Actavis is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraphs 26 and 27 of Plaintiff's Amended Complaint. Therefore, Actavis denies the allegations in those paragraphs.

15. In answer to the allegations contained in paragraph 28 of Plaintiff's Amended Complaint, Actavis admits that metoclopramide has the pharmacological effects set forth in the FDA approved package insert. Actavis denies the remaining allegations in paragraph 28 of Plaintiff's Amended Complaint.

16. Actavis is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraphs 29 through 40 of Plaintiff's Amended Complaint. Therefore, Actavis denies the allegations in those paragraphs.

ALLEGATIONS

17. The allegations contained in paragraph 41 of Plaintiff's Amended Complaint are definitional statements to which no response is necessary by this answering Defendant, but to the extent that this paragraph alleges allegations against Actavis, these allegations are denied.

18. Actavis denies the allegations contained in paragraph 42 of Plaintiff's Amended Complaint.

Reglan/Metoclopramide: Indications and Resulting Side Effects

19. Actavis admits the allegations contained in paragraph 43 of Plaintiff's Amended Complaint.

20. Actavis denies the allegations contained in paragraph 44 of Plaintiff's Amended Complaint.

21. Actavis is without knowledge or information sufficient to form a belief as to the truth of allegations contained in paragraphs 45 through 48 of Plaintiff's Amended Complaint. Therefore, Actavis denies the allegations contained in paragraphs 45 through 48 of Plaintiff's Amended Complaint.

22. Actavis admits that tardive dyskinesia is a neurological disorder that can result in movement disorders and denies the remaining allegations in paragraph 49 of Plaintiff's Amended Complaint for want of information, knowledge, and otherwise.

23. Actavis is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraphs 50 through 51 of Plaintiff's Amended Complaint. Therefore, Actavis denies the allegations in paragraphs 50 through 51 of Plaintiff's Amended Complaint.

Defendant Wyeth as Successor in Interest to Reglan's Innovator

24. Actavis is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 52 of Plaintiff's Amended Complaint. Therefore, Actavis denies the allegations

contained in paragraph 52 of Plaintiff's Amended Complaint.

25. The allegations in paragraphs 53 through 60 of Plaintiff's Amended Complaint are not directed to this Defendant. To the extent that they might be construed as such, Actavis denies all such allegations for want of information, knowledge, and otherwise.

Defendant Schwarz Knowingly Acquired Metoclopramide's Risks

26. The allegations in paragraphs 61 through 63 of Plaintiff's Amended Complaint are not directed to this Defendant. To the extent that they might be construed as such, Actavis denies all such allegations for want of information, knowledge, and otherwise.

Defendant Wyeth & Schwarz[] [Allegedly] Failed to Act as Required by the FDA

27. The allegations in paragraph 64 through 81 of Plaintiff's Amended Complaint are not directed to this Defendant. To the extent that they might be construed as such, Actavis denies all such allegations for want of information, knowledge, and otherwise.

Generic Defendants [Allegedly] Failed to Act as Required by the FDA

28. Paragraph 82 of Plaintiff's Amended Complaint is a definitional paragraph to which no response is necessary, but to the extent that this paragraph may be construed as directing allegations against Actavis, such allegations are denied.

29. Actavis admits the allegations in paragraph 83 of Plaintiff's Amended Complaint.

30. In response to paragraphs 84 and 85 of Plaintiff's Amended Complaint, Actavis responds that these paragraphs call for a legal conclusion to which no response is necessary, but to the extent that these paragraphs assert allegations against Actavis, such allegations are denied. Further answering, Defendant states that FDA regulations require it to use the brand name approved labeling at all times.

31. Actavis denies the allegations contained in paragraphs 86 through 90 of Plaintiff's Amended Complaint.

DEFENDANTS [Allegedly] Failed to Meet Labeling & Packaging Insert Requirements

32. Actavis denies the allegations contained in paragraphs 91 through 94 of Plaintiff's Amended Complaint.

DEFENDANTS [Allegedly] Failed to Disclose Known, Serious Side Effects

33. Actavis denies the allegations contained in paragraph 95 of Plaintiff's Amended Complaint as directed against it and is without knowledge sufficient to form a belief as to the truth of these allegations as directed to the other defendants.

34. Actavis denies the allegations contained in paragraphs 96 through 105 of Plaintiff's Amended Complaint.

COUNT I

STRICT PRODUCTS LIABILITY

35. In response to paragraph 106 of Plaintiff's Amended Complaint, Actavis restates and realleges paragraphs 1 through 34 of its Answer to Plaintiff's Amended Complaint.

36. Actavis denies the allegations contained in paragraphs 107 to 115 of Plaintiff's Amended Complaint.

COUNT II

BREACH OF EXPRESS WARRANTY

37. In response to paragraph 116 of Plaintiff's Amended Complaint, Actavis restates and realleges paragraphs 1 through 36 of its Answer to Plaintiff's Amended Complaint.

38. Actavis denies the allegations contained in paragraphs 117 to 121 of Plaintiff's Amended Complaint.

COUNT III

BREACH OF IMPLIED WARRANTIES

39. In response to paragraph 122 of Plaintiff's Amended Complaint, Actavis restates and realleges paragraphs 1 through 38 of its Answer to Plaintiff's Amended Complaint.

40. Actavis denies the allegations contained in paragraphs 123 to 128 of Plaintiff's Amended Complaint.

COUNT IV

NEGLIGENCE

41. In response to paragraph 129 of Plaintiff's Amended Complaint, Actavis restates and realleges paragraphs 1 through 40 of its Answer to Plaintiff's Amended Complaint.

42. Actavis denies the allegations contained in paragraphs 130 to 134 of Plaintiff's Amended Complaint.

COUNT V

MISREPRESENTATION BY OMISSION

43. In response to paragraph 135 of Plaintiff's Amended Complaint, Actavis restates and realleges paragraphs 1 through 42 of its Answer to Plaintiff's Amended Complaint.

44. Actavis denies the allegations contained in paragraphs 136 to 147 of Plaintiff's Amended Complaint.

COUNT VI

CONSTRUCTIVE FRAUD

45. In response to paragraph 148 of Plaintiff's Amended Complaint, Actavis restates and realleges

paragraphs 1 through 44 of its Answer to Plaintiff's Amended Complaint.

46. Actavis denies the allegations contained in paragraphs 149 to 153 of Plaintiff's Amended Complaint.

COUNT VII

MINNESOTA DECEPTIVE TRADE PRACTICE ACT

47. In response to paragraph 154 of Plaintiff's Amended Complaint, Actavis restates and realleges paragraphs 1 through 46 of its Answer to Plaintiff's Amended Complaint.

48. Actavis denies the allegations contained in paragraphs 155 to 163 of Plaintiff's Amended Complaint.

COUNT VIII

MINNESOTA FALSE STATEMENT IN ADVERTISINIG ACT

49. In response to paragraph 164 of Plaintiff's Amended Complaint, Actavis restates and realleges paragraphs 1 through 48 of its Answer to Plaintiff's Amended Complaint.

50. Actavis denies the allegations contained in paragraphs 165 to 169 of Plaintiff's Amended Complaint.

COUNT IX

MINNESOTA PREVENTION OF CONSUMER FRAUD ACT

51. In response to paragraph 170 of Plaintiff's Amended Complaint, Actavis restates and realleges paragraphs 1 through 50 of its Answer to Plaintiff's Amended Complaint.

52. Actavis denies the allegations contained in paragraphs 171 to 175 of Plaintiff's Amended Complaint.

COUNT X

INTENTIONAL INFLICTION OF EMOTIONAL DISTRESS

53. In response to paragraph 176 of Plaintiff's Amended Complaint, Actavis restates and realleges paragraphs 1 through 52 of its Answer to Plaintiff's Amended Complaint.

54. Actavis denies the allegations contained in paragraphs 177 to 179 of Plaintiff's Amended Complaint.

COUNT XI

NEGLIGENT INFLICTION OF EMOTIONAL DISTRESS

55. In response to paragraph 180 of Plaintiff's Amended Complaint, Actavis restates and realleges

paragraphs 1 through 54 of its Answer to Plaintiff's Amended Complaint.

56. Actavis denies the allegations contained in paragraphs 181 to 184 of Plaintiff's Amended Complaint.

COUNT XII

NEGLIGENT MISREPRESENTATION

57. In response to paragraph 185 of Plaintiff's Amended Complaint, Actavis restates and realleges paragraphs 1 through 56 of its Answer to Plaintiff's Amended Complaint.

58. Actavis denies the allegations contained in paragraphs 186 to 191 of Plaintiff's Amended Complaint.

COUNT XIII

FRAUD BY CONCEALMENT

59. In response to paragraph 192 of Plaintiff's Amended Complaint, Actavis restates and realleges paragraphs 1 through 58 of its Answer to Plaintiff's Amended Complaint.

60. Actavis denies the allegations contained in paragraphs 193 to 197 of Plaintiff's Amended Complaint.

COUNT XIV

JOINT AND SEVERAL LIABILITY

61. In response to paragraph 198 of Plaintiff's Amended Complaint, Actavis restates and realleges paragraphs 1 through 60 of its Answer to Plaintiff's Amended Complaint.

62. Actavis denies the allegations contained in paragraph 199 of Plaintiff's Amended Complaint.

DAMAGES

63. Actavis denies the allegations contained in paragraphs 200 through 203 of Plaintiff's Amended Complaint.

PRAYER FOR RELIEF

64. In response to the WHEREFORE clause contained on page 31 of Plaintiff's Amended Complaint, Actavis denies that Plaintiff is entitled to any of the relief sought therein, and specifically denies that Plaintiff is entitled to the relief sought in subparagraphs 1 through 7 contained therein.

AFFIRMATIVE DEFENSES

65. Plaintiff's Amended Complaint fails to state a claim upon which relief may be granted.

66. Plaintiff's fraud claims are barred due to her failure to plead the circumstances constituting the alleged fraud with particularity as required by Fed. R. Civ. P. 9(b).

67. Plaintiff's Amended Complaint is barred for failure to join indispensable parties.

68. Plaintiff assumed the risk of her alleged damages.

69. Plaintiff, Gladys Mensing, was negligent and her negligence should be compared with that of the Defendants, which negligence is specifically denied, to reduce or bar her claims as set forth in Minnesota Statutes section 604.01.

70. Plaintiff's alleged damages were caused by her failure to exercise ordinary care to follow the advice, information, warnings and instructions provided with any product marketed by Actavis.

71. Plaintiff's alleged injuries and damages, if any, were the result of the misuse of the subject pharmaceutical product at issue. Defendant further alleges that if Plaintiff suffered injuries attributable to the Plaintiff's use of the subject pharmaceutical product at issue in this suit, which allegations are expressly denied, the injuries, if any, were solely caused and attributable to the unreasonable, unforeseeable and improper use of said pharmaceutical product by the Plaintiff and/or third parties.

72. Plaintiff's alleged damages were caused by the negligence or other fault of persons or entities other than Actavis who are not within the control of Actavis and for whom Actavis has no liability.

73. Plaintiff's alleged damages resulted from new and independent, unforeseeable, superseding and/or

intervening causes unrelated to any conduct of, or product placed in the stream of commerce by, Actavis.

74. Plaintiff's alleged damages were the result of preexisting conditions unrelated to any conduct of, or product placed in the stream of commerce by, Actavis.

75. Actavis provided adequate and complete warnings to Plaintiff's prescribing physicians. Any claim made by Plaintiff for inadequate warnings accordingly is barred by the learned intermediary doctrine.

76. Reglan® and/or generic metoclopramide was designed, tested, manufactured, and marketed in conformance with the state of the scientific, medical and technological art and knowledge existing at the time of sale and, accordingly, Plaintiff's claims are barred.

77. Plaintiff's claims are barred, in whole or in part, because Actavis complied with all applicable statutes and with the requirements and regulations of the Food and Drug Administration and all of Plaintiff's claims are therefore barred, in whole or in part, by the Supremacy Clause of the United States Constitution, Article IV, clause 2, and the laws of the United States. Specifically, Plaintiff's failure to warn claims are preempted by federal food and drug regulations specifying that the warning language that can be used by generic manufacturers must be exactly the same as that approved by the FDA for use by the innovator manufacturer.

78. Plaintiff's claims are barred in whole or in part because there is no private right of action

concerning matters regulated by the Food and Drug Administration under applicable federal laws, regulations, and rules.

79. The warning, labeling, advertising, and sale of the subject pharmaceutical product at issue complied at all times with the FDCA, 21 U.S.C. § 300 *et seq.* and the Federal Trade Commission Act, 15 U.S.C. § 41 *et seq.* Consequently, Plaintiff's Complaint is preempted by these acts and compliance with these acts constitutes a complete or partial defense to the allegations of Plaintiff's Complaint against Defendant, including any claim for punitive damages. Alternatively, Defendant is entitled to a presumption that the subject pharmaceutical product at issue is not defective or unreasonably dangerous and that it's labeling was adequate.

80. Defendant alleges that the pharmaceutical product at issue was fit and proper for its intended purpose and that the utility of the subject pharmaceutical product at issue outweighs any possible risk inherent in the use of the subject pharmaceutical product.

81. Defendant is informed and believes and thereon alleges that Plaintiff failed to provide Defendant with timely notice of any alleged nonconformance with any express representation.

82. To the extent that Plaintiff seeks punitive damages for the conduct which allegedly caused injuries asserted in the Complaint, punitive damages are barred or reduced by applicable law or statute or, in the alternative, are unconstitutional insofar as they violate the due process protections afforded by the

United States Constitution, the excessive fines clause of the Eighth Amendment of the United States Constitution, the Commerce Clause of the United States Constitution, the Full Faith and Credit Clause of the United States Constitution, and applicable provisions of the Constitution of the State of Minnesota. Any law, statute, or other authority purporting to permit the recovery of punitive damages in this case is unconstitutional, facially and as applied, to the extent that, without limitation, it: (1) lacks constitutionally sufficient standards to guide and restrain the jury's discretion in determining whether to award punitive damages and/or the amount, if any; (2) is void for vagueness in that it failed to provide adequate advance notice as to what conduct will result in punitive damages; (3) permits recovery of punitive damages based on out-of-state conduct, conduct that complied with applicable law, or conduct that was not directed, or did not proximately cause harm, to Plaintiff; (4) permits recovery of punitive damages in an amount that is not both reasonable and proportionate to the amount of harm, if any, to Plaintiff and to the amount of compensatory damages, if any; (5) permits jury consideration of net worth or other financial information relating to this Defendant; (6) lacks constitutionally sufficient standards to be applied by the trial court in post-verdict review of any punitive damages awards; (7) lacks constitutionally sufficient standards for appellate review of punitive damages awards; and (8) otherwise fails to satisfy Supreme Court precedent.

83. Plaintiff's claims are barred because she would have taken the subject pharmaceutical product even if the subject pharmaceutical product's labeling

contained the information that Plaintiff contends should have been provided.

84. Plaintiff's claims are barred, in whole or in part, because the advertisements, if any, and labeling with respect to the subject pharmaceutical product were not false or misleading and, therefore, constitute protected commercial speech under the applicable provisions of the United States Constitution.

85. Defendant made no warranties of any kind, express or implied, or any representations of any nature whatsoever to Plaintiff herein. Additionally, as a manufacturer and not a seller, Defendant is not subject to liability for implied warranties without privity, i.e., proof of direct and specific transactions between the Plaintiff and Defendant. If any such warranties were made, whether express or implied, which Defendant specifically denies, then Plaintiff failed to give timely notice of any breach thereof.

86. Plaintiff's claims against Actavis are barred by Restatement (Second) of Torts Section 402A and the comments thereto, and by the Restatement (Third) of Torts Product Liability §§ 4 and 6, *et. seq.*

87. Neither Plaintiff nor Plaintiff's respective physicians were induced to prescribe or use Reglan® and/or generic metoclopramide based on any material representations or misrepresentations of Actavis.

88. Plaintiff did not rely on any express or implied warranty allegedly made by Actavis.

89. Plaintiff's alleged damages were caused in whole or in part by Plaintiff's failure to mitigate such damages.

90. Plaintiff's causes of action may be barred, in whole or in part, by the doctrines of laches, waiver, and estoppel.

91. Plaintiff's causes of action may be barred, in whole or in part, by the applicable statute of limitations.

92. Plaintiff impermissibly seeks to impose liability on conduct protected from liability by the First Amendment to the United States Constitution.

93. In the absence of proof by Plaintiff that the product used and ingested by Plaintiff was made or distributed by Actavis, Actavis may not be held liable for any claim herein.

94. Actavis expressly reserves the right to assert any additional affirmative defenses that may become apparent through discovery in this case and expressly reserves the right to amend its Answer to assert any such affirmative defenses.

WHEREFORE, Actavis respectfully requests dismissal of Plaintiff's claims and an award of costs, interests, fees and such other and further relief as the Court deems necessary and proper.

TRIAL BY JURY IS HEREBY DEMANDED

Pursuant to Rule 38(b) of the Federal Rules of Civil Procedure, Defendant Actavis Elizabeth LLC. hereby

restates its demand for a trial by jury, composed of the maximum number of jurors allowed by law, on all of the issues in this case.

Dated: March 11, 2008

Respectfully submitted,

s/Bradley J. Lindeman
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Actavis Elizabeth LLC

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[Certificate of Service omitted in printing of this appendix]

* * *

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF MINNESOTA

CASE NO. 07-CV-3919
DWF/SRN

[Filed March 13, 2008]

GLADYS MENSING,	)
	)
Plaintiff,	)
	)
v.	)
	)
WYETH, INC. (d/b/a WYETH); SCHWARZ PHARMA, INC,.; PLIVA, INC.; TEVA PHARMACEUTICALS, USA, INC.; ALPHARMA, INC., d/b/a ALPHARMA PHARMACEUTICALS; UDL LABORATORIES, INC.; ACTAVIS ELIZABETH, LLC, and PUREPAC PHARMACEUTICAL CO.,	)
	)
Defendants.	)
	)

PLIVA, INC.'S ANSWER, DEFENSES, AND JURY DEMAND TO PLAINTIFF'S FIRST AMENDED COMPLAINT

PLIVA, Inc., answers plaintiff's First Amended Complaint ("Complaint") as follows:

I. PARTIES

1. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 1 of the Complaint.

2. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 2 of the Complaint.

3. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 3 of the Complaint.

4. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 4 of the Complaint.

5. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 5 of the Complaint.

6. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 6 of the Complaint.

7. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 7 of the Complaint.

8. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 8 of the Complaint.

9. PLIVA, Inc., admits that its principal place of business is in New Jersey. PLIVA, Inc., denies the remaining allegations in paragraph 9 of the Complaint.

10. PLIVA, Inc., admits that it has engaged in the testing, manufacture, sale, and distribution of generic metoclopramide. PLIVA, Inc., admits that it may be served through its agent for service of process, The Corporation Trust Company, located at 820 Bear Tavern Road, 3rd Floor, West Trenton, New Jersey 08628. PLIVA, Inc., denies the remaining allegations in paragraph 10 of the Complaint.

11. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 11 of the Complaint.

12. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 12 of the Complaint.

13. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 13 of the Complaint.

14. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 14 of the Complaint.

15. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 15 of the Complaint.

16. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 16 of the Complaint.

17. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 17 of the Complaint.

18. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 18 of the Complaint.

19. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 19 of the Complaint.

20. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 20 of the Complaint.

21. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 21 of the Complaint.

22. PLIVA, Inc., admits that plaintiff purports to refer to all defendants collectively as the "Defendants."

23. PLIVA, Inc., denies the allegations in paragraph 23 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 23 of the Complaint that are directed to other defendants.

24. PLIVA, Inc., admits that is has engaged in the testing, manufacture, and distribution of generic metoclopramide. PLIVA, Inc., denies the remaining allegations in paragraph 24 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of

the allegations in paragraph 24 of the Complaint that are directed to other defendants.

II. VENUE AND JURISDICTION

25. PLIVA, Inc., denies the allegations in paragraph 25 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge sufficient to form a belief as to the truth of the allegations in paragraph 25 of the Complaint that are directed to other defendants.

III. FACTUAL BACKGROUND

26. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 26 of the Complaint.

27. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 27 of the Complaint.

28. PLIVA, Inc., admits that metoclopramide has the pharmacological effects set forth in its FDA-approved package insert. PLIVA, Inc., denies the remaining allegations in paragraph 28 of the Complaint.

29. PLIVA, Inc., admits that metoclopramide has the pharmacological effects set forth in its FDA-approved package insert. PLIVA, Inc., denies the remaining allegations in paragraph 29 of the Complaint.

30. PLIVA, Inc., admits that metoclopramide has the pharmacological effects set forth in its FDA-approved package insert. PLIVA, Inc., denies the

remaining allegations in paragraph 30 of the Complaint.

31. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 31 of the Complaint.

32. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 32 of the Complaint.

33. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 33 of the Complaint.

34. PLIVA, Inc., denies the allegations in paragraph 34 of the Complaint.

35. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 35 of the Complaint.

36. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 36 of the Complaint.

37. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 37 of the Complaint.

38. PLIVA, Inc., denies the allegations in paragraph 38 of the Complaint.

39. PLIVA, Inc., denies the allegations in paragraph 39 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information

sufficient to form a belief as to the truth of the allegations in paragraph 39 of the Complaint that are directed to other defendants.

40. PLIVA, Inc., denies the allegations in paragraph 40 of the Complaint.

IV. ALLEGATIONS

41. PLIVA, Inc., denies the allegations in paragraph 41 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 41 of the Complaint that are directed to other defendants.

42. PLIVA, Inc., denies the allegations in paragraph 42 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 42 of the Complaint that are directed to other defendants.

Reglan/Metoclopramide: Indications and Resulting Side Effects

43. PLIVA, Inc., states that metoclopramide is approved for the indications set forth in the FDA-approved package insert for Reglan. PLIVA, Inc., denies that paragraph 43 of the Complaint completely or accurately characterizes the FDA-approved package insert for metoclopramide. PLIVA, Inc., denies the remaining allegations in paragraph 43 of the Complaint.

44. PLIVA, Inc., states that metoclopramide is approved for the indications set forth in the FDA-approved package insert for Reglan. PLIVA, Inc., denies that paragraph 44 of the Complaint completely or accurately characterizes the FDA-approved package insert for metoclopramide. PLIVA, Inc., denies the remaining allegations in paragraph 44 of the Complaint.

45. PLIVA, Inc., admits that the risks of metoclopramide are set forth in the FDA-approved package insert for Reglan. PLIVA, Inc., denies that paragraph 45 of the Complaint completely or accurately characterizes the FDA-approved package insert for metoclopramide. PLIVA, Inc., denies the remaining allegations in paragraph 45 of the Complaint.

46. PLIVA, Inc., states that the side effects of metoclopramide are set forth in the FDA-approved package insert for Reglan. PLIVA, Inc., denies that paragraph 46 of the Complaint completely or accurately characterizes the FDA-approved package insert for metoclopramide. PLIVA, Inc., denies the remaining allegations in paragraph 46 of the Complaint.

47. PLIVA, Inc., states that the risks of metoclopramide are set forth in the FDA-approved package insert for Reglan. PLIVA, Inc., denies that paragraph 47 of the Complaint completely or accurately characterizes the FDA-approved package insert for metoclopramide. PLIVA, Inc., denies the remaining allegations in paragraph 47 of the Complaint.

48. PLIVA, Inc., states that the risks of metoclopramide are set forth in the FDA-approved package insert for Reglan. PLIVA, Inc., denies that paragraph 48 of the Complaint completely or accurately characterizes the FDA-approved package insert for metoclopramide. PLIVA, Inc., denies the remaining allegations in paragraph 48 of the Complaint.

49. PLIVA, Inc., denies that paragraph 49 of the Complaint completely or accurately characterizes the symptoms of tardive dyskinesia. PLIVA, Inc., denies the remaining allegations in paragraph 49 of the Complaint.

50. PLIVA, Inc., denies that paragraph 50 of the Complaint completely or accurately characterizes the prognosis for tardive dyskinesia patients. PLIVA, Inc., denies the remaining allegations in paragraph 50 of the Complaint.

51. PLIVA, Inc., denies the allegations in paragraph 51 of the Complaint.

Defendant Wyeth as Successor in Interest to Reglan's Innovator

52. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 52 of the Complaint, including footnote 1

53. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 53 of the Complaint.

54. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 54 of the Complaint.

55. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 55 of the Complaint.

56. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 56 of the Complaint.

57. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 57 of the Complaint, including footnote 2.

58. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 58 of the Complaint.

59. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 59 of the Complaint.

60. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 60 of the Complaint.

Defendant Schwarz Knowingly Acquired Metoclopramide's Risks

61. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 61 of the Complaint.

62. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 62 of the Complaint, including footnote 3.

63. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 63 of the Complaint.

Defendants Wyeth & Schwarz Failed to Act as Required by the FDA

64. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 64 of the Complaint.

65. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 65 of the Complaint.

66. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 66 of the Complaint.

67. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 67 of the Complaint.

68. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 68 of the Complaint.

69. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 69 of the Complaint.

70. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 70 of the Complaint.

71. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 71 of the Complaint.

72. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 72 of the Complaint.

73. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 73 of the Complaint.

74. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 74 of the Complaint.

75. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 75 of the Complaint.

76. PLIVA, Inc., states that the Hatch-Waxman Act and state law regarding pharmaceutical products speak for themselves. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the remaining allegations in paragraph 76 of the Complaint.

77. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 77 of the Complaint.

78. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 78 of the Complaint.

79. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 79 of the Complaint.

80. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 80 of the Complaint.

81. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 81 of the Complaint.

Generic Defendants Failed to Act as Required by the FDA

82. PLIVA, Inc., admits that it submitted two Abbreviated New Drug Applications ("ANDA") for Metoclopramide Tablets USP to the United States Food and Drug Administration, ANDA application number 72-750 for 5 mg. Metoclopramide Tablets USP, and ANDA application number 71-250 for 10 mg. Metoclopramide Tablets USP. PLIVA, Inc., admits that plaintiff purports to refer to PLIVA, Inc.; Teva Pharmaceuticals, USA, Inc.; UDL Laboratories, Inc.; Actavis Elizabeth LLC; Purepac Pharmaceutical Co.; Wyeth "by and through ESI;" and Fictitious Parties 1-6, collectively, as the "Generic Defendants." PLIVA, Inc., denies the remaining allegations in paragraph 82 of the Complaint.

83. PLIVA, Inc., admits that the ANDA process is governed by applicable provisions of the Code of

Federal Regulations ("CFR"), which include provisions dealing with labeling. PLIVA, Inc., admits that it complied with all applicable CFR sections governing drug labeling in its ANDA application number 72-750 and ANDA application number 71-250. PLIVA, Inc., denies that paragraph 83 of the Complaint fully and accurately sets forth the relevant CFR provisions governing the ANDA process. PLIVA, Inc., denies the remaining allegations in paragraph 83 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 83 of the Complaint that are directed to other defendants.

84. PLIVA, Inc., admits that the manufacture and distribution of ANDA products is governed by applicable provisions of the CFR. PLIVA, Inc., admits that it complied with all applicable CFR sections with respect to products manufactured under its ANDA application number 72-750 and ANDA application number 71-250. PLIVA, Inc., denies that paragraph 84 of the Complaint fully and accurately sets forth the relevant CFR provisions governing the ANDA process. PLIVA, Inc., denies the remaining allegations in paragraph 84 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 84 of the Complaint that are directed to other defendants.

85. PLIVA, Inc., admits that the manufacture and distribution of ANDA products is governed by applicable provisions of the CFR. PLIVA, Inc., admits that it complied with all applicable CFR sections with respect to products manufactured under its ANDA application number 72-750 and ANDA application

number 71-250. PLIVA, Inc., denies that paragraph 85 of the Complaint fully and accurately sets forth the relevant CFR provisions governing the ANDA process. PLIVA, Inc., denies the remaining allegations in paragraph 85 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 85 of the Complaint that are directed to other defendants.

86. PLIVA, Inc., denies the allegations in paragraph 86 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 86 of the Complaint that are directed to other defendants.

87. PLIVA, Inc., denies the allegations in paragraph 87 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 87 of the Complaint that are directed to other defendants.

88. PLIVA, Inc., denies the allegations in paragraph 88 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 88 of the Complaint that are directed to other defendants.

89. Paragraph 89 of the Complaint states conclusions of law to which no response is required or necessary. To the extent a response is required, PLIVA, Inc., admits that the manufacture and distribution of ANDA products is governed by

applicable provisions of the CFR, which include provisions dealing with labeling. PLIVA, Inc., admits that it complied with all applicable CFR sections with respect to products manufactured under its ANDA application number 72-750 and ANDA application number 71-250. PLIVA, Inc., denies that paragraph 89 of the Complaint fully and accurately sets forth the relevant CFR provisions governing the ANDA process. PLIVA, Inc., denies the remaining allegations in paragraph 89 of the Complaint.

90. PLIVA, Inc., denies the allegations in paragraph 90 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 90 of the Complaint that are directed to other defendants.

Defendants Failed to meet Labeling & Packaging Insert Requirements

91. PLIVA, Inc., denies the allegations in paragraph 91 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 91 of the Complaint that are directed to other defendants.

92. PLIVA, Inc., denies the allegations in paragraph 92 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 92 of the Complaint that are directed to other defendants.

93. PLIVA, Inc., denies the allegations in paragraph 93 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 93 of the Complaint that are directed to other defendants.

94. Paragraph 94 of the Complaint states conclusions of law to which no response is required or necessary. To the extent a response is required, PLIVA, Inc., denies the allegations in paragraph 94 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 94 of the Complaint that are directed to other defendants.

Defendants Failed to Disclose Known, Serious Side Effects

95. PLIVA, Inc., denies the allegations in paragraph 95 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 95 of the Complaint that are directed to other defendants.

96. PLIVA, Inc., denies the allegations in paragraph 96 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 96 of the Complaint that are directed to other defendants.

97. PLIVA, Inc., denies the allegations in paragraph 97 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information

sufficient to form a belief as to the truth of the allegations in paragraph 97 of the Complaint that are directed to other defendants.

98. PLIVA, Inc., denies the allegations in paragraph 98 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 98 of the Complaint that are directed to other defendants.

99. PLIVA, Inc., denies the allegations in paragraph 99 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 99 of the Complaint that are directed to other defendants.

100. PLIVA, Inc., denies the allegations in paragraph 100 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 100 of the Complaint that are directed to other defendants.

101. PLIVA, Inc., denies the allegations in paragraph 101 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 101 of the Complaint that are directed to other defendants.

102. PLIVA, Inc., denies the allegations in paragraph 102 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the

allegations in paragraph 102 of the Complaint that are directed to other defendants.

103. PLIVA, Inc., denies the allegations in paragraph 103 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 103 of the Complaint that are directed to other defendants.

104. PLIVA, Inc., denies the allegations in paragraph 104 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 104 of the Complaint that are directed to other defendants.

105. PLIVA, Inc., denies the allegations in paragraph 105 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 105 of the Complaint that are directed to other defendants.

V. WRONGFUL CONDUCT

COUNT 1
STRICT PRODUCTS LIABILITY

106. PLIVA, Inc., denies each and every allegation in the Complaint, except as admitted above.

107. PLIVA, Inc., denies the allegations in paragraph 107 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the

allegations in paragraph 107 of the Complaint that are directed to other defendants.

108. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations regarding whether metoclopramide reached plaintiff without substantial change in its condition. PLIVA, Inc., denies the remaining allegations in paragraph 109 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 108 of the Complaint that are directed to other defendants.

109. PLIVA, Inc., denies the allegations in paragraph 109 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 109 of the Complaint that are directed to other defendants.

110. PLIVA, Inc., denies the allegations in paragraph 110 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 110 of the Complaint that are directed to other defendants.

111. PLIVA, Inc., denies the allegations in paragraph 111 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 111 of the Complaint that are directed to other defendants.

112. PLIVA, Inc., denies the allegations in paragraph 112 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 112 of the Complaint that are directed to other defendants.

113. PLIVA, Inc., denies the allegations in paragraph 113 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 113 of the Complaint that are directed to other defendants.

114. PLIVA, Inc., denies the allegations in paragraph 114 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 114 of the Complaint that are directed to other defendants.

115. PLIVA, Inc., denies the allegations in paragraph 115 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 115 of the Complaint that are directed to other defendants.

COUNT 2
BREACH OF EXPRESS WARRANTY

116. PLIVA, Inc., denies each and every allegation in the Complaint, except as admitted above.

117. PLIVA, Inc., denies the allegations in paragraph 117 of the Complaint that are directed to it.

PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 117 of the Complaint that are directed to other defendants.

118. PLIVA, Inc., denies the allegations in paragraph 118 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 118 of the Complaint that are directed to other defendants.

119. PLIVA, Inc., denies the allegations in paragraph 119 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 119 of the Complaint that are directed to other defendants.

120. PLIVA, Inc., denies the allegations in paragraph 120 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 120 of the Complaint that are directed to other defendants.

121. PLIVA, Inc., denies the allegations in paragraph 121 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 121 of the Complaint that are directed to other defendants.

COUNT 3
BREACH OF IMPLIED WARRANTTIES

122. PLIVA, Inc., denies each and every allegation in the Complaint, except as admitted above.

123. PLIVA, Inc., denies the allegations in paragraph 123 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 123 of the Complaint that are directed to other defendants.

124. PLIVA, Inc., denies the allegations in paragraph 124 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 124 of the Complaint that are directed to other defendants.

125. PLIVA, Inc., denies the allegations in paragraph 125 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 125 of the Complaint that are directed to other defendants.

126. PLIVA, Inc., denies the allegations in paragraph 126 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 126 of the Complaint that are directed to other defendants.

127. PLIVA, Inc., denies the allegations in paragraph 127 of the Complaint that are directed to it.

PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 127 of the Complaint that are directed to other defendants.

128. PLIVA, Inc., denies the allegations in paragraph 128 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 128 of the Complaint that are directed to other defendants.

COUNT 4
NEGLIGENCE

129. PLIVA, Inc., denies each and every allegation in the Complaint, except as admitted above.

130. Paragraph 130 of the Complaint states conclusions of law to which no response is required or necessary. To the extent a response is required, PLIVA, Inc., denies the allegations in paragraph 130 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 130 of the Complaint that are directed to other defendants.

131. PLIVA, Inc., denies the allegations in paragraph 131 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 131 of the Complaint that are directed to other defendants.

132. PLIVA, Inc., denies the allegations in paragraph 132 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 132 of the Complaint that are directed to other defendants.

133. PLIVA, Inc., denies the allegations in paragraph 133 of the Complaint, including subsections (a) through (e), that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 133 of the Complaint, including subsections (a) through (e), that are directed to other defendants.

134. PLIVA, Inc., admits that plaintiff purports to plead the doctrine of *res ipsa loquitur*, but denies that the doctrine is appropriate. PLIVA, Inc., denies the remaining allegations in paragraph 134 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 134 of the Complaint that are directed to other defendants.

COUNT 5
MISREPRESENTATION BY OMISSION

135. PLIVA, Inc., denies each and every allegation in the Complaint, except as admitted above.

136. PLIVA, Inc., denies the allegations in paragraph 136 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the

allegations in paragraph 136 of the Complaint that are directed to other defendants.

137. PLIVA, Inc., denies the allegations in paragraph 137 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 137 of the Complaint that are directed to other defendants.

138. PLIVA, Inc., denies the allegations in paragraph 138 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 138 of the Complaint that are directed to other defendants.

139. PLIVA, Inc., denies the allegations in paragraph 139 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 139 of the Complaint that are directed to other defendants.

140. PLIVA, Inc., denies the allegations in paragraph 140 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 140 of the Complaint that are directed to other defendants.

141. PLIVA, Inc., denies the allegations in paragraph 141 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the

allegations in paragraph 141 of the Complaint that are directed to other defendants.

142. PLIVA, Inc., denies the allegations in paragraph 142 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 142 of the Complaint that are directed to other defendants.

143. PLIVA, Inc., denies the allegations in paragraph 143 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 143 of the Complaint that are directed to other defendants.

144. PLIVA, Inc., denies the allegations in paragraph 144 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 144 of the Complaint that are directed to other defendants.

145. PLIVA, Inc., denies the allegations in paragraph 145 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 145 of the Complaint that are directed to other defendants.

146. PLIVA, Inc., denies the allegations in paragraph 146 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the

allegations in paragraph 146 of the Complaint that are directed to other defendants.

147. PLIVA, Inc., denies the allegations in paragraph 147 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 147 of the Complaint that are directed to other defendants.

COUNT 6
CONSTRUCTIVE FRAUD

148. PLIVA, Inc., denies each and every allegation in the Complaint, except as admitted above.

149. PLIVA, Inc., denies the allegations in paragraph 149 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 149 of the Complaint that are directed to other defendants.

150. PLIVA, Inc., denies the allegations in paragraph 150 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 150 of the Complaint that are directed to other defendants.

151. PLIVA, Inc., denies the allegations in paragraph 151 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 151 of the Complaint that are directed to other defendants.

152. PLIVA, Inc., denies the allegations in paragraph 152 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 152 of the Complaint that are directed to other defendants.

153. PLIVA, Inc., denies the allegations in paragraph 153 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 153 of the Complaint that are directed to other defendants.

COUNT 7
VIOLATION OF THE MINNESOTA DECEPTIVE TRACE PRACTICE ACT [SIC]

154. PLIVA, Inc., denies each and every allegation in the Complaint, except as admitted above.

155. PLIVA, Inc., denies the allegations in paragraph 155 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 155 of the Complaint that are directed to other defendants.

156. PLIVA, Inc., denies the allegations in paragraph 156 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 156 of the Complaint that are directed to other defendants.

157. PLIVA, Inc., denies the allegations in paragraph 157 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 157 of the Complaint that are directed to other defendants.

158. PLIVA, Inc., denies the allegations in paragraph 158 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 158 of the Complaint that are directed to other defendants.

159. PLIVA, Inc., denies the allegations in paragraph 159 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 159 of the Complaint that are directed to other defendants.

160. PLIVA, Inc., denies the allegations in paragraph 160 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 160 of the Complaint that are directed to other defendants.

161. PLIVA, Inc., denies the allegations in paragraph 161 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 161 of the Complaint that are directed to other defendants.

162. PLIVA, Inc., denies the allegations in paragraph 162 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 162 of the Complaint that are directed to other defendants.

163. PLIVA, Inc., denies the allegations in paragraph 163 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 163 of the Complaint that are directed to other defendants.

COUNT 8
VIOLATION OF THE MINNESOTA FALSE STATEMENT IN ADVERTISING ACT

164. PLIVA, Inc., denies each and every allegation in the Complaint, except as admitted above.

165. PLIVA, Inc., denies the allegations in paragraph 165 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 165 of the Complaint that are directed to other defendants.

166. PLIVA, Inc., denies the allegations in paragraph 166 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 166 of the Complaint that are directed to other defendants.

167. PLIVA, Inc., denies the allegations in paragraph 167 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 167 of the Complaint that are directed to other defendants.

168. PLIVA, Inc., denies the allegations in paragraph 168 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 168 of the Complaint that are directed to other defendants.

169. PLIVA, Inc., denies the allegations in paragraph 169 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 169 of the Complaint that are directed to other defendants.

COUNT 9
VIOLATION OF THE MINNESOTA PREVENTION OF CONSUMER FRAUD ACT

170. PLIVA, Inc., denies each and every allegation in the Complaint, except as admitted above.

171. PLIVA, Inc., denies the allegations in paragraph 171 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 171 of the Complaint that are directed to other defendants.

172. PLIVA, Inc., denies the allegations in paragraph 172 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 172 of the Complaint that are directed to other defendants.

173. PLIVA, Inc., denies the allegations in paragraph 173 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 173 of the Complaint that are directed to other defendants.

174. PLIVA, Inc., denies the allegations in paragraph 174 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 174 of the Complaint that are directed to other defendants.

175. PLIVA, Inc., denies the allegations in paragraph 175 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 175 of the Complaint that are directed to other defendants.

COUNT 10
INTENTIONAL INFLICTION OF EMOTIONAL DISTRESS

176. PLIVA, Inc., denies each and every allegation in the Complaint, except as admitted above.

177. PLIVA, Inc., denies the allegations in paragraph 177 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 177 of the Complaint that are directed to other defendants.

178. PLIVA, Inc., denies the allegations in paragraph 178 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 178 of the Complaint that are directed to other defendants.

179. PLIVA, Inc., denies the allegations in paragraph 179 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 179 of the Complaint that are directed to other defendants.

COUNT 11
NEGLIGENT INFLICTION
OF EMOTIONAL DISTRESS

180. PLIVA, Inc., denies each and every allegation in the Complaint, except as admitted above.

181. PLIVA, Inc., denies the allegations in paragraph 181 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 181 of the Complaint that are directed to other defendants.

182. PLIVA, Inc., denies the allegations in paragraph 182of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 182 of the Complaint that are directed to other defendants.

183. PLIVA, Inc., denies the allegations in paragraph 183 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 183 of the Complaint that are directed to other defendants.

184. PLIVA, Inc., denies the allegations in paragraph 184 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 184 of the Complaint that are directed to other defendants.

COUNT 12
NEGLIGENT MISREPRESENTATION

185. PLIVA, Inc., denies each and every allegation in the Complaint, except as admitted above.

186. PLIVA, Inc., denies the allegations in paragraph 186 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 186 of the Complaint that are directed to other defendants.

187. Paragraph 187 of the Complaint states conclusions of law to which no response is required or

necessary. To the extent a response is required, PLIVA, Inc., denies the allegations in paragraph 187 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 187 of the Complaint that are directed to other defendants.

188. Paragraph 188 of the Complaint states conclusions of law to which no response is required or necessary. To the extent a response is required, PLIVA, Inc., denies the allegations in paragraph 188 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 188 of the Complaint that are directed to other defendants.

189. PLIVA, Inc., denies the allegations in paragraph 189 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 189 of the Complaint that are directed to other defendants.

190. PLIVA, Inc., denies the allegations in paragraph 190 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 190 of the Complaint that are directed to other defendants.

191. PLIVA, Inc., denies the allegations in paragraph 191 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the

allegations in paragraph 191 of the Complaint that are directed to other defendants.

COUNT 13
FRAUD BY CONCEALMENT

192. PLIVA, Inc., denies each and every allegation in the Complaint, except as admitted above.

193. PLIVA, Inc., denies the allegations in paragraph 193 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 193 of the Complaint that are directed to other defendants.

194. PLIVA, Inc., denies the allegations in paragraph 194 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 194 of the Complaint that are directed to other defendants.

195. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations regarding what plaintiff's physician did or why. PLIVA, Inc., denies the remaining allegations in paragraph 195 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 195 of the Complaint that are directed to other defendants.

196. PLIVA, Inc., denies the allegations in paragraph 196 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information

sufficient to form a belief as to the truth of the allegations in paragraph 196 of the Complaint that are directed to other defendants.

197. PLIVA, Inc., denies the allegations in paragraph 197 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 197 of the Complaint that are directed to other defendants.

COUNT 14
JOINT AND SEVERAL LIABILITY

198. PLIVA, Inc., denies each and every allegation in the Complaint, except as admitted above.

199. PLIVA, Inc., denies the allegations in paragraph 199 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 199 of the Complaint that are directed to other defendants.

VI. DAMAGES

200. PLIVA, Inc., denies the allegations in paragraph 200 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 200 of the Complaint that are directed to other defendants.

201. PLIVA, Inc., denies the allegations in paragraph 201 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information

sufficient to form a belief as to the truth of the allegations in paragraph 201 of the Complaint that are directed to other defendants.

202. PLIVA, Inc., denies the allegations in paragraph 202 of the Complaint that are directed to it. PLIVA, Inc., is without knowledge or information sufficient to form a belief as to the truth of the allegations in paragraph 202 of the Complaint that are directed to other defendants.

203. PLIVA, Inc., admits that plaintiff seeks the relief requested in paragraph 203 of the Complaint, but denies that plaintiff is entitled to the same, or any recovery whatsoever.

PRAYER FOR RELIEF

PLIVA, Inc., admits that plaintiff seeks the relief requested in the paragraph of the Complaint beginning, "WHEREFORE," including all sub-parts, but denies that plaintiff is entitled to the relief requested, or any recovery whatsoever.

DEFENSES

Pleading further, PLIVA, Inc., asserts the following defenses to the Complaint and reserves its right to amend or supplement these defenses as further information becomes available through discovery:

1. The Complaint fails to state a claim upon which relief can be granted.

2. Plaintiff's Complaint should be dismissed for improper venue.

3. Plaintiff's Complaint should be dismissed because there is no personal jurisdiction over defendant PLIVA, Inc.

4. This Court lacks subject matter jurisdiction over plaintiff's claims.

5. Plaintiff has failed to join all necessary and appropriate parties.

6. PLIVA, Inc., is not a proper party-defendant.

7. Plaintiff has failed to plead her claims with sufficient particularity.

8. Plaintiff lacks standing and/or capacity to assert the claims alleged in the Complaint.

9. Plaintiff's claims are barred by the doctrine of unclean hands, laches, waiver and/or estoppel.

10. Any claim or cause of action that plaintiff may have had is barred by the applicable statutes of limitation and/or statues of repose.

11. Lack of privity between plaintiff and PLIVA bars any claims based on contractual or warranty theories.

12. The product at issue in this litigation has been formulated, designed, tested, manufactured, processed, distributed, and labeled in accordance with the provisions of the federal Food, Drug and Cosmetic Act and any regulations promulgated thereunder. Therefore, plaintiff's claims are preempted or barred by federal law and regulation.

13. Plaintiff's claims are barred because at the time the product at issue in this litigation left PLIVA, Inc.'s control, it complied with applicable codes, standards, regulations, and specifications established, adopted, promulgated, or approved by the United States or by Minnesota law, or by any agency of the United States or Minnesota. The product was reasonably fit, suitable, and safe for its intended purpose.

14. The product at issue in this litigation was modified, altered, or changed from the condition in which it was sold, which modification, alteration, or change caused or contributed to cause plaintiff's alleged damages.

15. The product at issue in this litigation conformed precisely in all ways to its specifications and performance standards and posed no danger in its manufacture and composition.

16. Plaintiff's claims are barred because at the time the product at issue in this litigation left PLIVA, Inc.'s control, a practical and technically feasible alternative design or formulation was not available that would have prevented the harm for which plaintiff seeks to recover damages without substantially impairing the reasonably anticipated or intended function of the product.

17. Plaintiff's damages, if any, were caused by inherent characteristics of the product that are generic aspects of the product that cannot be eliminated without substantially compromising the product's usefulness or desirability. Further, all reasonable precautions consistent with legal duties and

obligations were taken to protect third parties from any dangers posed by the inherent characteristics of the product.

18. The benefits of the product outweigh the risk of danger or harm, if any, inherent in the product.

19. There is no duty to warn about any possible dangers that were not known at the time of manufacture and sale of product in question.

20. Any communications and/or actions between any of the defendants and the United States Food and Drug Administration and/or any governmental agency or entity are constitutionally protected under the Noerr-Pennington Doctrine and the First Amendment to the United States Constitution.

21. The product at issue in this litigation was sold in a reasonable and prudent manner based upon available medical and scientific knowledge and further were processed in accordance with and pursuant to all applicable regulations of the Federal Food and Drug Administration.

22. Based on the state of scientific, medical, and technological knowledge at the time they were marketed, the product at issue in this litigation was reasonably safe for their normal and foreseeable uses. In light of the existing reasonably available medical, scientific, and technological knowledge, the design characteristics, if any, that allegedly caused the damages plaintiff complains of, or the alleged risk of such characteristics, could not have been known.

23. PLIVA, Inc.'s actions conformed to the state of the art of reasonably available scientific and technological knowledge at all times relevant to this lawsuit. At the time the product left the control of PLIVA, Inc., the product was in conformity with the generally recognized state of the art applicable to the safety of the product at the time the product was designed, manufactured, packaged, or labeled.

24. PLIVA, Inc., at all times discharged its duty to warn through appropriate and adequate warnings in accordance with federal statutes and regulations consistent with the existing state of medical and scientific knowledge.

25. The advertisements, if any, with respect to the product at issue were not false or misleading and, therefore, constitute protected commercial speech under the applicable provisions of the United States and applicable state constitutions.

26. If plaintiff sustained damages by reason of the matters alleged in the Complaint, which is denied, then said damages were caused solely by or contributed to by the acts or fault of third parties and were not caused or contributed to by any acts or fault of PLIVA, Inc., its officers, agents, contractors, servants, employees, or others for whom it was responsible.

27. Plaintiff's damages, if any, were proximately caused by unforeseeable, independent, intervening, or superseding events beyond the control, and unrelated to the conduct of PLIVA, Inc. The actions and omissions of PLIVA, Inc., if any, were superseded by

such unforeseeable, independent, intervening, and superseding events.

28. The injuries and damages claimed by plaintiff resulted from her own conduct so that plaintiff's claims are barred, in whole or in part, by the comparative negligence, fault, or responsibility of causation attributed to plaintiff. Thus, plaintiff's claims should be dismissed, reduced, offset, or barred in accordance with the principles of comparative negligence. Plaintiff's recovery of damages, if any exist, must be reduced by the comparative negligence and/or fault of plaintiff and other persons, including responsible non-parties, pursuant to Minnesota law.

29. The injuries and damages claimed by plaintiff were caused, in whole or in part, by the acts or omissions of persons other than PLIVA, Inc., over whom PLIVA, Inc., had no control. Therefore, any recovery by plaintiff should be apportioned in direct proportion to such fault in accordance with applicable law.

30. Any injuries or damages sustained by plaintiff were directly and proximately caused by the failure of plaintiff to heed warnings and instructions. Therefore, no recovery is available to plaintiff.

31. If plaintiff sustained damages as alleged in the Complaint, which is denied, plaintiff failed to mitigate her damages.

32. Plaintiff's misuse of the product, which was not reasonably foreseeable, caused plaintiff's alleged damages, if any, and plaintiff's claims therefore may be barred or reduced by applicable law.

33. Plaintiff's claims are barred to the extent the injuries alleged in the Complaint were caused or enhanced by pre-existing or unrelated medical, genetic, environmental, or psychiatric conditions, diseases or illnesses, by plaintiff's own idiosyncratic reactions, and/or by operation of nature.

34. Plaintiff's claims are barred on the grounds that plaintiff knew, or in the exercise of ordinary care should have known, of the risks of the injuries or damages alleged in the Complaint, if any, and nevertheless, did freely and voluntarily assume said risks, and in this undertaking proximately caused and contributed to the losses, injuries, or damage, if any, alleged by plaintiff.

35. Plaintiff's claims against PLIVA, Inc., are barred by the learned-intermediary doctrine.

36. Plaintiff is barred, in whole or in part, from recovery due to spoliation of evidence.

37. There is no responsibility for either the acts or omissions of the knowledgeable users or misinformation or lack of information provided to the plaintiffs by others.

38. With respect to each and every cause of action, plaintiffs are not entitled to recover because of the delay and the fundamental unfairness and prejudice due to the excessive delay from the date of the alleged use of the products allegedly sold by PLIVA, Inc., and the filing of the Complaint.

39. There were no warranties, either express or implied, between plaintiff and PLIVA, Inc.

40. PLIVA, Inc., breached no warranties, either express or implied, which may have existed between it and plaintiff.

41. Plaintiff failed to give notice of any alleged breach of any warranty as required by state law and is, therefore, barred from any recovery for such claims.

42. The express and implied warranties alleged to have been made were expressly disclaimed and excluded by the label; any and all statements made concerning the product referred to in the Complaint applied only when used as directed.

43. To the extent plaintiff seeks exemplary or punitive damages, the Complaint fails to allege facts sufficient to entitle plaintiff to an award of exemplary or punitive damages.

44. To the extent plaintiff seeks exemplary or punitive damages, such damages are prohibited under the Fifth, Eighth, and Fourteenth Amendments of the United States Constitution and are limited or barred by Minnesota law.

45. To the extent plaintiff seeks exemplary or punitive damages, PLIVA, Inc., specifically incorporates by reference all standards and/or limitations regarding the determination and enforceability of punitive damage awards which arise in the decisions of *BMW of North America v. Gore*, 517 U.S. 559 (1996), *Cooper Industries, Inc. v. Leatherman Tool Group, Inc.*, 532 U.S. 424 (2001), and *State Farm Mut. Auto. Ins. Co. v. Campbell*, 123 S. Ct. 1513, 1519, 1521 (2003).

46. To the extent that the claims stated in the Complaint have been settled, compromised, or otherwise discharged, a set off is due.

47. Plaintiff fails to state a claim upon which attorneys' fees can be awarded.

48. PLIVA, Inc., adopts and relies upon all provisions and defenses afforded it under Restatement of Torts 2d, § 402A, including the comments thereto.

49. PLIVA, Inc., reserves the right to raise all defenses provided in sections 2, 4, and 6 of the Restatement (Third) of Torts: Product Liability, if the Court finds that it is applicable in this case.

50. PLIVA, Inc., incorporates all defenses available under Minnesota's liability law.

51. Plaintiff's claims, if any, are barred, reduced and/or limited pursuant to any other applicable limitations of awards, caps on recovery, and setoffs permitted by law, including, but not limited to Minnesota law regarding noneconomic loss or injury, and applicable Minnesota law related to amounts paid or provided by collateral sources.

52. PLIVA, Inc., adopts and relies upon all provisions and defenses afforded it under the United States Constitution and the Minnesota Constitution.

53. The product that is at issue in this litigation was not in an unreasonably dangerous condition.

54. PLIVA, Inc.'s conduct was not the proximate or producing cause of plaintiff's alleged injuries, if any.

55. PLIVA, Inc.'s product was not defective in manufacture, design, construction, or formulation, and it conformed to all representations made by PLIVA, Inc., if any.

56. If plaintiff suffered or sustained any injuries, loss, or damage as a result of the alleged incident referred to in plaintiff's Complaint, the same were a direct result of plaintiff's failure to follow the reasonable advice of her health care providers.

57. The injuries or damages sustained by plaintiff, if any, may be attributed to several causes and accordingly should be apportioned among the various causes according to the respective contribution of each such cause to the harm sustained.

58. Plaintiff failed to exercise ordinary care under the circumstances in using the product and such failure was the substantial cause of the occurrence that caused injury or damage, if any, to plaintiff.

59. Plaintiff's claims are barred by additional defenses that may arise during the course of this litigation, which PLIVA, Inc., reserves the right to assert.

60. PLIVA, Inc., incorporates the defenses of all others who are or may become parties to this action as though more fully set forth herein.

JURY DEMAND

A TRIAL BY JURY IS DEMANDED.

Dated: March 13, 2008

HALLELAND LEWIS NILAN & JOHNSON, P.A.

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JAN 24 2011

Nos. 09-993 vide 09-1039, 09-1501

In the Supreme Court of the United States

PLIVA, Inc., et al., 09-993 vide 09-1039, *Petitioners*,

v.

Gladys Mensing, *Respondent*.

Actavis Elizabeth, LLC, 09-1039 vide 09-993, *Petitioner*,

v.

Gladys Mensing, *Respondent*.

Actavis, Inc., 09-1501, *Petitioner*,

v.

Julie Demahy, *Respondent*.

On Writs of Certiorari to the United States Courts of Appeals for the Fifth and Eighth Circuits

JOINT APPENDIX, Volume 2

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January 24, 2011 *(counsel continued on inside cover)*

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Petitions for Writ of Certiorari granted December 10, 2010

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UNITED STATES DISTRICT COURT
DISTRICT OF MINNESOTA

Case No. 0:07-cv-03919-DWF-XXX

[Filed March 13, 2008]

GLADYS MENSING	)
	)
Plaintiff	)
	)
v.	)
	)
WYETH, INC. et al.,	)
	)
Defendants.	)
	)

ANSWER OF TEVA PHARMACEUTICALS USA, INC. TO PLAINTIFF'S FIRST AMENDED COMPLAINT

JURY TRIAL DEMANDED

Defendant Teva Pharmaceuticals USA, Inc. ("Teva"), by its attorneys, Felhaber, Larson, Fenlon & Vogt PA, as and for its Answer to the First Amended Complaint herein:

PRELIMINARY STATEMENT

Many of the paragraphs of the First Amended Complaint and of the individual allegations contained therein are addressed jointly to Teva and the other "Defendants," as that term is defined in the First Amended Complaint, or without distinction between

them. Teva and the other Defendants are unrelated corporate entities. In general, Teva has no knowledge, actual, constructive or otherwise, as to actions, conduct, business practices or corporate behavior of the other Defendants. Accordingly, in the responses that follow, Teva responds solely on its own behalf, and denies knowledge or information as to the truth or falsity of any and all allegations as to the other Defendants, except insofar as expressly averred otherwise.

Teva responds to the individual paragraphs of the First Amended Complaint as follows:

1. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 1 of the First Amended Complaint.

2. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 2 of the First Amended Complaint, except denies each and every such allegation insofar as it is alleged or implied that plaintiff was injured or otherwise suffered any damages as a result of any culpable conduct of Teva.

3. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 3 of the First Amended Complaint.

4. In response to paragraph 4 of the First Amended Complaint, admits that references in the First Amended Complaint to "Wyeth" may include individually and collectively all divisions and/or

subsidiaries, Wyeth as successor in interest to A.H. Robins, Inc., American Home Drugs Corporation, and ESI.

5. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 5 of the First Amended Complaint.

6. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 6 of the First Amended Complaint, except admits upon information and belief that metoclopramide manufactured by Wyeth was sold with an ESI Lederle, Inc. label.

7. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 7 of the First Amended Complaint.

8. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 8 of the First Amended Complaint.

9. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 9 of the First Amended Complaint.

10. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 10 of the First Amended Complaint.

11. Admits each and every allegation contained in paragraph 11 of the First Amended Complaint.

12. Denies each and every allegation contained in paragraph 12 of the First Amended Complaint, except admits that, from time to time, Teva has manufactured and sold in interstate commerce a generic form of metoclopramide for human use, including for use in the State of Minnesota, and that Teva's registered agent is Corporate Creations, located at 11380 Prosperity Farms Road #221E, Palm Beach Gardens, FL 33410; Teva does not contest proper service of this action.

13. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 13 of the First Amended Complaint.

14. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 14 of the First Amended Complaint.

15. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 15 of the First Amended Complaint.

16. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 16 of the First Amended Complaint.

17. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the

allegations contained in paragraph 17 of the First Amended Complaint.

18. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 18 of the First Amended Complaint.

19. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 19 of the First Amended Complaint.

20. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 20 of the First Amended Complaint.

21. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 21 of the First Amended Complaint.

22. In response to paragraph 22 of the First Amended Complaint, admits that Defendants are sometimes referred to collectively in the First Amended Complaint as the "Defendants."

23. Neither admits nor denies the allegations contained in paragraph 23 of the First Amended Complaint to the extent that they purport to state conclusions of law, except admits that Teva is a corporation and necessarily acts through its officers and employees.

24. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 24 of the First Amended Complaint, except admits that, from time to time, Teva has manufactured and sold in interstate commerce a generic form of metoclopramide for human use, including for use in the State of Minnesota.

25. Denies each and every allegation contained in paragraph 25 of the First Amended Complaint, except admits that, from time to time, Teva has manufactured and sold in interstate commerce a generic form of metoclopramide for human use, including for use in the State of Minnesota, and further neither admits nor denies the allegations contained in paragraph 25 of the First Amended Complaint to the extent that they purport to state conclusions of law.

26. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 26 of the First Amended Complaint.

27. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 27 of the First Amended Complaint.

28. Admits upon information and belief each and every allegation contained in paragraph 28 of the First Amended Complaint.

29. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the

allegations contained in paragraph 29 of the First Amended Complaint.

30. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 30 of the First Amended Complaint.

31. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 31 of the First Amended Complaint.

32. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 32 of the First Amended Complaint.

33. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 33 of the First Amended Complaint, except denies that plaintiff used metoclopramide in accordance with its recommended directions for use.

34. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 34 of the First Amended Complaint, except denies each and every allegation insofar as it is alleged or implied that any injuries or damages suffered by plaintiff resulted from culpable conduct of Teva.

35. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 35 of the First

Amended Complaint, except denies each and every allegation insofar as it is alleged or implied that any injuries or damages suffered by plaintiff resulted from culpable conduct of Teva.

36. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 36 of the First Amended Complaint.

37. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 37 of the First Amended Complaint.

38. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 38 of the First Amended Complaint, except denies each and every such allegation insofar as it is alleged or implied that any injuries or damages suffered by plaintiff resulted from culpable conduct of Teva.

39. Denies each and every allegation contained in paragraph 39 of the First Amended Complaint.

40. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 40 of the First Amended Complaint, except denies each and every allegation insofar as it is alleged or implied that any injuries or damages suffered by plaintiff resulted from culpable conduct of Teva.

41. Denies each and every allegation contained in paragraph 41 of the First Amended Complaint,

except admits that the allegations in paragraph 41 of the First Amended Complaint purport to state plaintiff's contentions in this lawsuit.

42. Denies each and every allegation contained in paragraph 42 of the First Amended Complaint, except admits that, from time to time, Teva has manufactured and sold in interstate commerce a generic form of metoclopramide for human use, including for use in the State of Minnesota.

43. Denies each and every allegation contained in paragraph 43 of the First Amended Complaint, except admits that metoclopramide is indicated for use as specified in its product labeling as approved from time to time by the FDA, and respectfully refers the Court to the labeling in force during the period of the plaintiff's alleged ingestion of metoclopramide for the terms thereof.

44. Denies each and every allegation contained in paragraph 44 of the First Amended Complaint, except admits that metoclopramide is indicated for use as specified in its product labeling as approved from time to time by the FDA, and respectfully refers the Court to the labeling in force during the period of the plaintiff's alleged ingestion of metoclopramide for the terms thereof.

45. Denies each and every allegation contained in paragraph 45 of the First Amended Complaint, except admits that the risk of developing tardive dyskinesia as a result of the use of metoclopramide may increase with the duration of treatment and total cumulative dose.

46. Denies each and every allegation contained in paragraph 46 of the First Amended Complaint, except admits that the use of metoclopramide can result in adverse reactions that may include, *inter alia*, central nervous system disorders, depression with suicidal ideation, akathesia, tardive dyskinesia, acute dystonia, and visual disturbances.

47. Denies each and every allegation contained in paragraph 47 of the First Amended Complaint, except admits that the risk of experiencing certain adverse reactions to the use of metoclopramide, including tardive dyskinesia, may be related to the duration of treatment and total cumulative dose.

48. Denies each and every allegation contained in paragraph 48 of the First Amended Complaint, except admits that the risk of experiencing certain adverse reactions to the use of metoclopramide, including tardive dyskinesia, may be related to the duration of treatment and total cumulative dose, and that diabetes may be a co-risk factor thereto.

49. Denies each and every allegation contained in paragraph 49 of the First Amended Complaint, except admits that tardive dyskinesia is a disorder typically involving involuntary movements of the facial muscles and tongue.

50. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 50 of the First Amended Complaint.

51. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the

allegations contained in paragraph 51 of the First Amended Complaint.

52. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 52 of the First Amended Complaint, except admits upon information and belief that A.H. Robins Company, Inc. was the first to obtain approval from the FDA of an NDA for metoclopramide, which it sold in the United States under the brand name Reglan®.

53. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 53 of the First Amended Complaint.

54. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 54 of the First Amended Complaint.

55. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 55 of the First Amended Complaint.

56. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 56 of the First Amended Complaint.

57. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 57 of the First Amended Complaint, except admits upon information

and belief that metoclopramide manufactured by Wyeth was sold with an ESI Lederle, Inc. label.

58. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 58 of the First Amended Complaint, except admits upon information and belief that as the holder of the NDA for Reglan®, the reference listed drug ("RLD") for Teva's metoclopramide products, Wyeth had such obligations to test, monitor and disclose information relating to the safety and efficacy of Reglan® as were imposed by and applicable from time to time under the U.S. Food, Drug and Cosmetic Act and the FDA's implementing regulations thereof.

59. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 59 of the First Amended Complaint.

60. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 60 of the First Amended Complaint, except admits upon information and belief that Wyeth prepared and disseminated full prescribing information for Reglan®, in the form, inter alia, of a package insert, in accordance with its FDA regulatory obligations, and caused such full prescribing information to be published from time to time in the PDR.

61. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 61 of the First Amended Complaint, except admits upon information

and belief that the NDA for Reglan® was transferred from Wyeth to Schwarz.

62. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 62 of the First Amended Complaint, except admits upon information and belief that the NDA for Reglan® was transferred from Wyeth to Schwarz.

63. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 63 of the First Amended Complaint, except denies that Teva's metoclopramide products were defective or otherwise accompanied by inadequate warnings.

64. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 64 of the First Amended Complaint, except admits upon information and belief that Schwarz is currently listed as the holder of the NDA for Reglan®, the RLD for Teva's metoclopramide products.

65. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 65 of the First Amended Complaint, except admits upon information and belief that Schwarz is currently listed as the holder of the NDA for Reglan®, the RLD for Teva's metoclopramide products.

66. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 66 of the First

Amended Complaint, except admits that Wyeth's and Schwarz's labeling of Reglan® disclosed that various extrapyramidal symptoms and other adverse reactions may be associated with the use of metoclopramide.

67. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 67 of the First Amended Complaint, except admits upon information and belief that as a holders of the NDA for Reglan®, Wyeth and Schwarz had such obligations to test, monitor and disclose information relating to the safety and efficacy of Reglan® as were imposed by and applicable from time to time under the U.S. Food, Drug and Cosmetic Act and the FDA's implementing regulations thereof.

68. Denies each and every allegation contained in paragraph 68 of the First Amended Complaint, except denies knowledge or information as to whether Wyeth, Schwarz, or their predecessors made any false or fraudulent allegations regarding Reglan®.

69. Denies each and every allegation contained in paragraph 69 of the First Amended Complaint, except denies knowledge or information as to whether Wyeth, Schwarz, or their predecessors made any false or fraudulent allegations regarding Reglan®.

70. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 70 of the First Amended Complaint, except denies each and every such allegation insofar as it is alleged or implied that any injuries or damages suffered by plaintiff resulted from culpable conduct of Teva.

71. Denies each and every allegation contained in paragraph 71 of the First Amended Complaint, except denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations as to what Wyeth and Schwarz had actual knowledge of.

72. Denies each and every allegation contained in paragraph 72 of the First Amended Complaint, except denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations as to what Wyeth and Schwarz had actual knowledge of.

73. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 73 of the First Amended Complaint, except denies each and every such allegation insofar as it is alleged or implied that any injuries or damages suffered by plaintiff resulted from culpable conduct of Teva.

74. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 74 of the First Amended Complaint, except denies that Teva's metoclopramide products were defective or otherwise accompanied by inadequate warnings.

75. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 75 of the First Amended Complaint, except denies that Teva's metoclopramide products were defective or otherwise accompanied by inadequate warnings.

76. Admits upon information and belief each and every allegation contained in paragraph 76 of the First Amended Complaint.

77. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 77 of the First Amended Complaint, except neither admits nor denies the allegations contained in paragraph 77 of the First Amended Complaint to the extent that they purport to state conclusions of law.

78. Denies each and every allegation contained in paragraph 78 of the First Amended Complaint, except admits that, pursuant to applicable federal statutory law and FDA regulations, Teva's package insert for its metoclopramide products is required to be, and has at all relevant times been, identical to the package insert for Reglan®, its "reference-listed drug," in the form in which the same was approved from time to time by the FDA, except for permissible differences as enumerated in 21 C.F.R. § 314.94.

79. Denies each and every allegation contained in paragraph 79 of the First Amended Complaint,

80. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 80 of the First Amended Complaint, except admits upon information and belief that, when seeking prescribing information for a drug, doctors commonly refer to the labeling, in the form of the package insert or PDR entry, for the "brand name" or reference listed drug product.

81. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 81 of the First Amended Complaint, except admits upon information and belief that, when seeking prescribing information for a drug, doctors commonly refer to the labeling, in the form of the package insert or PDR entry, for the "brand name" or reference listed drug product.

82. Denies each and every allegation contained in paragraph 82 of the First Amended Complaint, except admits that Teva and a predecessor in interest to Teva submitted Abbreviated New Drug Applications to the U.S. Food and Drug Administration for authorization to manufacture and sell metoclopramide products.

83. Denies each and every allegation contained in paragraph 83 of the First Amended Complaint, except admits that the U.S. Food, Drug and Cosmetic Act and implementing FDA regulations thereunder applicable to drugs manufactured and/or sold pursuant to the ANDA process require that product labeling for such drugs conform at all times to the label for the pertinent reference listed drug, except for enumerated permissible differences.

84. Denies each and every allegation contained in paragraph 84 of the First Amended Complaint, except admits that, as the holder of an ANDA for metoclopramide, Teva had such obligations with respect to post-marketing safety surveillance of the drug as were imposed by and applicable from time to time under the U.S. Food, Drug and Cosmetic Act and the FDA's implementing regulations thereof.

85. Denies each and every allegation contained in paragraph 85 of the First Amended Complaint, except admits that if an ANDA holder becomes aware of medical evidence supporting a need for a change to the product label, the FDA's expectation of best practices is that the ANDA holder will present such evidence to the FDA for it to act upon in consultation with the sponsor of the reference listed drug.

86. Denies each and every allegation contained in paragraph 86 of the First Amended Complaint, except admits that pursuant to applicable Food and Drug Administration regulations Teva was not required to and did not independently verify the safety and efficacy of metoclopramide for its FDA-approved indications.

87. Denies each and every allegation contained in paragraph 87 of the First Amended Complaint, except admits that applicable Food and Drug Administration regulations and accepted industry practice did not require Teva to conduct systematic reviews of relevant medical literature.

88. Denies each and every allegation contained in paragraph 88 of the First Amended Complaint, except admits that applicable Food and Drug Administration regulations as well as FDA standard practices contemplated that the manufacturer of the reference-listed drug would conduct systematic literature searches and report relevant medical literature to the FDA.

89. Denies each and every allegation contained in paragraph 89 of the First Amended Complaint, except admits that if the FDA directs the NDA holder

to amend its label, the ANDA holder is required to conform its label to the amended label for the reference listed drug.

90. Denies each and every allegation contained in paragraph 90 of the First Amended Complaint.

91. Denies each and every allegation contained in paragraph 91 of the First Amended Complaint, except admits that every shipping unit of Teva metoclopramide was accompanied by informational labeling, in the form of the package insert as approved from time to time by the FDA.

92. Denies each and every allegation contained in paragraph 92 of the First Amended Complaint.

93. Denies each and every allegation contained in paragraph 93 of the First Amended Complaint.

94. Denies each and every allegation contained in paragraph 94 of the First Amended Complaint, except admits that it had an obligation to manufacture, test, label, package, distribute and market its metoclopramide products in accordance with its FDA-approved Abbreviated New Drug Applications ("ANDA") therefor, all applicable FDA current Good Manufacturing Practices, and all other applicable FDA regulations and provisions of the Food, Drug & Cosmetic Act.

95. Denies each and every allegation contained in paragraph 95 of the First Amended Complaint, except admits that, as specified in the product labeling, as approved from time to time by the FDA, Teva's

metoclopramide products were indicated for the treatment of GERD and diabetic gastroparesis.

96. Denies each and every allegation contained in paragraph 96 of the First Amended Complaint.

97. Denies each and every allegation contained in paragraph 97 of the First Amended Complaint.

98. Denies each and every allegation contained in paragraph 98 of the First Amended Complaint.

99. Denies each and every allegation contained in paragraph 99 of the First Amended Complaint.

100. Denies each and every allegation contained in paragraph 100 of the First Amended Complaint.

101. Denies each and every allegation contained in paragraph 101 of the First Amended Complaint.

102. Denies each and every allegation contained in paragraph 102 of the First Amended Complaint.

103. Denies each and every allegation contained in paragraph 103 of the First Amended Complaint.

104. Denies each and every allegation contained in paragraph 104 of the First Amended Complaint.

105. Denies each and every allegation contained in paragraph 105 of the First Amended Complaint.

106. In response to paragraph 106 of the First Amended Complaint, repeats and realleges each and every response to paragraphs 1 through 105 of the

First Amended Complaint as though hereinafter fully set forth at length.

107. Denies each and every allegation contained in paragraph 107 of the First Amended Complaint.

108. Denies each and every allegation contained in paragraph 108 of the First Amended Complaint, except admits that, if plaintiff ingested metoclopramide manufactured by Teva, she was expected to ingest it in the same form in which it was manufactured and shipped, but denies knowledge or information as to whether she did so.

109. Denies each and every allegation contained in paragraph 109 of the First Amended Complaint.

110. Denies each and every allegation contained in paragraph 110 of the First Amended Complaint.

111. Denies each and every allegation contained in paragraph 111 of the First Amended Complaint.

112. Denies each and every allegation contained in paragraph 112 of the First Amended Complaint.

113. Denies each and every allegation contained in paragraph 113 of the First Amended Complaint.

114. Denies each and every allegation contained in paragraph 114 of the First Amended Complaint.

115. Denies each and every allegation contained in paragraph 115 of the First Amended Complaint.

116. In response to paragraph 116 of the First Amended Complaint, repeats and realleges each and every response to paragraphs 1 through 115 of the First Amended Complaint as though hereinafter fully set forth at length.

117. Denies each and every allegation contained in paragraph 117 of the First Amended Complaint.

118. Denies each and every allegation contained in paragraph 118 of the First Amended Complaint, except denies knowledge or information as to what plaintiff or her physicians relied upon.

119. Denies each and every allegation contained in paragraph 119 of the First Amended Complaint.

120. Denies each and every allegation contained in paragraph 120 of the First Amended Complaint.

121. Denies each and every allegation contained in paragraph 121 of the First Amended Complaint.

122. In response to paragraph 122 of the First Amended Complaint, repeats and realleges each and every response to paragraphs 1 through 121 of the First Amended Complaint as though hereinafter fully set forth at length.

123. Denies each and every allegation contained in paragraph 123 of the First Amended Complaint, except admits that, from time to time, Teva has manufactured and sold a generic form of metoclopramide for human use, admits that, as specified in the product labeling as approved from time to time by the FDA, Teva's metoclopramide products

were indicated for the treatment of GERD and diabetic gastroparesis, and further admits that Teva's metoclopramide products were safe and effective for use in accordance with their FDA-approved indications and directions for use.

124. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 124 of the First Amended Complaint, except denies each and every such allegation insofar as it is alleged or implied that any injuries or damages suffered by plaintiff resulted from culpable conduct of Teva.

125. Denies each and every allegation contained in paragraph 125 of the First Amended Complaint.

126. Denies each and every allegation contained in paragraph 126 of the First Amended Complaint.

127. Denies each and every allegation contained in paragraph 127 of the First Amended Complaint.

128. Denies each and every allegation contained in paragraph 128 of the First Amended Complaint.

129. In response to paragraph 129 of the First Amended Complaint, repeats and realleges each and every response to paragraphs 1 through 128 of the First Amended Complaint as though hereinafter fully set forth at length.

130. Denies each and every allegation contained in paragraph 130 of the First Amended Complaint, except admits that it had an obligation to manufacture, test, label, package, distribute and market its

metoclopramide products in accordance with its FDA-approved Abbreviated New Drug Applications ("ANDA") therefor, all applicable FDA current Good Manufacturing Practices, and all other applicable FDA regulations and provisions of the Food, Drug & Cosmetic Act.

131. Denies each and every allegation contained in paragraph 131 of the First Amended Complaint.

132. Denies each and every allegation contained in paragraph 132 of the First Amended Complaint.

133. Denies each and every allegation contained in paragraph 133 of the First Amended Complaint.

134. Denies each and every allegation contained in paragraph 134 of the First Amended Complaint.

135. In response to paragraph 135 of the First Amended Complaint, repeats and realleges each and every response to paragraphs 1 through 134 of the First Amended Complaint as though hereinafter fully set forth at length.

136. Denies each and every allegation contained in paragraph 136 of the First Amended Complaint.

137. Denies each and every allegation contained in paragraph 137 of the First Amended Complaint.

138. Denies each and every allegation contained in paragraph 138 of the First Amended Complaint.

139. Denies each and every allegation contained in paragraph 139 of the First Amended Complaint.

140. Denies each and every allegation contained in paragraph 140 of the First Amended Complaint.

141. Denies each and every allegation contained in paragraph 141 of the First Amended Complaint.

142. Denies each and every allegation contained in paragraph 142 of the First Amended Complaint.

143. Denies each and every allegation contained in paragraph 143 of the First Amended Complaint.

144. Denies each and every allegation contained in paragraph 144 of the First Amended Complaint.

145. Denies each and every allegation contained in paragraph 145 of the First Amended Complaint.

146. Denies each and every allegation contained in paragraph 146 of the First Amended Complaint.

147. Denies each and every allegation contained in paragraph 147 of the First Amended Complaint.

148. In response to paragraph 148 of the First Amended Complaint, repeats and realleges each and every response to paragraphs 1 through 147 of the First Amended Complaint as though hereinafter fully set forth at length.

149. Denies each and every allegation contained in paragraph 149 of the First Amended Complaint.

150. Denies each and every allegation contained in paragraph 150 of the First Amended Complaint.

151. Denies each and every allegation contained in paragraph 151 of the First Amended Complaint.

152. Denies each and every allegation contained in paragraph 152 of the First Amended Complaint.

153. Denies each and every allegation contained in paragraph 153 of the First Amended Complaint.

154. In response to paragraph 154 of the First Amended Complaint, repeats and realleges each and every response to paragraphs 1 through 153 of the First Amended Complaint as though hereinafter fully set forth at length.

155. Denies each and every allegation contained in paragraph 155 of the First Amended Complaint.

156. Denies each and every allegation contained in paragraph 156 of the First Amended Complaint.

157. Denies each and every allegation contained in paragraph 157 of the First Amended Complaint.

158. Denies each and every allegation contained in paragraph 158 of the First Amended Complaint.

159. Denies each and every allegation contained in paragraph 159 of the First Amended Complaint.

160. Denies each and every allegation contained in paragraph 160 of the First Amended Complaint.

161. Denies each and every allegation contained in paragraph 161 of the First Amended Complaint.

162. Denies each and every allegation contained in paragraph 162 of the First Amended Complaint.

163. Denies each and every allegation contained in paragraph 163 of the First Amended Complaint.

164. In response to paragraph 164 of the First Amended Complaint, repeats and realleges each and every response to paragraphs 1 through 163 of the First Amended Complaint as though hereinafter fully set forth at length.

165. Denies each and every allegation contained in paragraph 165 of the First Amended Complaint.

166. Denies each and every allegation contained in paragraph 166 of the First Amended Complaint.

167. Denies each and every allegation contained in paragraph 167 of the First Amended Complaint.

168. Denies each and every allegation contained in paragraph 168 of the First Amended Complaint.

169. Denies each and every allegation contained in paragraph 169 of the First Amended Complaint.

170. In response to paragraph 170 of the First Amended Complaint, repeats and realleges each and every response to paragraphs 1 through 169 of the First Amended Complaint as though hereinafter fully set forth at length.

171. Denies each and every allegation contained in paragraph 171 of the First Amended Complaint.

172. Denies each and every allegation contained in paragraph 172 of the First Amended Complaint.

173. Denies each and every allegation contained in paragraph 173 of the First Amended Complaint.

174. Denies each and every allegation contained in paragraph 174 of the First Amended Complaint.

175. Denies each and every allegation contained in paragraph 175 of the First Amended Complaint.

176. In response to paragraph 176 of the First Amended Complaint, repeats and realleges each and every response to paragraphs 1 through 175 of the First Amended Complaint as though hereinafter fully set forth at length.

177. Denies each and every allegation contained in paragraph 177 of the First Amended Complaint.

178. Denies each and every allegation contained in paragraph 178 of the First Amended Complaint.

179. Denies each and every allegation contained in paragraph 179 of the First Amended Complaint.

180. In response to paragraph 180 of the First Amended Complaint, repeats and realleges each and every response to paragraphs 1 through 179 of the First Amended Complaint as though hereinafter fully set forth at length.

181. Denies each and every allegation contained in paragraph 181 of the First Amended Complaint.

182. Denies each and every allegation contained in paragraph 182 of the First Amended Complaint.

183. Denies each and every allegation contained in paragraph 183 of the First Amended Complaint.

184. Denies each and every allegation contained in paragraph 184 of the First Amended Complaint.

185. In response to paragraph 185 of the First Amended Complaint, repeats and realleges each and every response to paragraphs 1 through 184 of the First Amended Complaint as though hereinafter fully set forth at length.

186. Denies each and every allegation contained in paragraph 186 of the First Amended Complaint.

187. Denies each and every allegation contained in paragraph 187 of the First Amended Complaint, except admits that Teva had an obligation to manufacture, test, label, package, distribute and market its metoclopramide products in accordance with its FDA-approved Abbreviated New Drug Applications ("ANDA") therefor, all applicable FDA current Good Manufacturing Practices, and all other applicable FDA regulations and provisions of the Food, Drug & Cosmetic Act.

188. Denies each and every allegation contained in paragraph 188 of the First Amended Complaint, except admits that it had an obligation to manufacture, test, label, package, distribute and market its metoclopramide products in accordance with its FDA-approved Abbreviated New Drug Applications ("ANDA") therefor, all applicable FDA current Good

Manufacturing Practices, and all other applicable FDA regulations and provisions of the Food, Drug & Cosmetic Act.

189. Denies each and every allegation contained in paragraph 189 of the First Amended Complaint.

190. Denies each and every allegation contained in paragraph 190 of the First Amended Complaint.

191. Denies each and every allegation contained in paragraph 191 of the First Amended Complaint.

192. In response to paragraph 192 of the First Amended Complaint, repeats and realleges each and every response to paragraphs 1 through 191 of the First Amended Complaint as though hereinafter fully set forth at length.

193. Denies each and every allegation contained in paragraph 193 of the First Amended Complaint.

194. Denies each and every allegation contained in paragraph 194 of the First Amended Complaint.

195. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 195 of the First Amended Complaint, except denies each and every allegation insofar as it is alleged or implied that any injuries or damages suffered by plaintiff resulted from culpable conduct of Teva.

196. Denies each and every allegation contained in paragraph 196 of the First Amended Complaint.

197. Denies each and every allegation contained in paragraph 197 of the First Amended Complaint.

198. In response to paragraph 198 of the First Amended Complaint, repeats and realleges each and every response to paragraphs 1 through 197 of the First Amended Complaint as though hereinafter fully set forth at length.

199. Denies each and every allegation contained in paragraph 199 of the First Amended Complaint.

200. Denies each and every allegation contained in paragraph 200 of the First Amended Complaint.

201. Denies each and every allegation contained in paragraph 201 of the First Amended Complaint.

202. Denies each and every allegation contained in paragraph 202 of the First Amended Complaint.

203. In response to paragraph 203 of the First Amended Complaint, admits that plaintiff seeks recovery for damages as alleged therein, but denies that Teva has any liability to plaintiff therefor.

AS AND FOR AFFIRMATIVE DEFENSES

204. Plaintiff's First Amended Complaint, and each and every allegation therein directed to Teva, fails to state a claim against Teva upon which relief may be granted.

205. Plaintiff's claims are barred in whole or in part by the applicable statutes of limitations.

206. Plaintiff's claims against Teva are barred by laches, waiver, and/or estoppel.

207. If plaintiff sustained any injury or incurred any loss or damage as alleged in the First Amended Complaint, the same resulted in whole or in part from an intervening cause and/or causes, and any action on the part of Teva was not the proximate and/or competent producing cause of plaintiff's alleged injuries.

208. If plaintiff sustained any injury or incurred any loss or damages as alleged in the First Amended Complaint, the same were caused in whole or in part by acts or omissions of another or others over whom Teva neither exercised nor had any right of control, for which Teva is and was not responsible, and whose conduct Teva had no duty or reason to anticipate or control.

209. If in fact the First Amended Complaint is held to contain a claim upon which relief may be granted, then plaintiff's recovery, if any, should be reduced by the relative amount of comparative fault attributable to plaintiff or her agents or persons other than Teva.

210. The manufacture, marketing and labeling of metoclopramide was controlled by federal law and Teva was at all times in compliance with applicable federal law with respect thereto; therefore, the First Amended Complaint fails to state a claim upon which relief may be granted in that, inter alia, such causes of action, if upheld, would impede, impair, frustrate or burden the effectiveness of federal law regulating the field of prescription items and would constitute an

invalid burden by this court on interstate commerce, and would, therefore, violate the Supremacy Clause (Article VI, Section 2) and the Commerce Clause (Article I, Section 8) of the United States Constitution.

211. In the event plaintiff is found to have suffered any injury, disease, damage, pain and/or disability, the degree of responsibility, negligence, and fault of each person who contributed to said injuries should be determined, and Teva should be held liable only for that proportion of the resulting damage which corresponds to its degree of fault, responsibility, or negligence, if any.

212. Any damages, injuries or losses that may have been sustained by plaintiff as alleged in the First Amended Complaint were sustained only after plaintiff knowingly and voluntarily assumed any alleged risk inherent in the use of metoclopramide.

213. Plaintiff failed to heed the warnings provided by Teva.

214. Teva is not a proper party.

215. Upon information and belief, any injury, loss or damage that plaintiff may have sustained was caused in whole or in part by plaintiff's own negligence.

216. If Teva is found liable to plaintiff for any non-economic loss allegedly suffered by plaintiff, such liability equals fifty percent or less of the total liability of all persons liable, and the aggregate liability of such other persons equals or exceeds fifty percent of the total liability. Accordingly, Teva's liability, if any, to

plaintiff for plaintiff's non-economic loss shall not exceed Teva's equitable share determined in accordance with the relative culpability of each person causing or contributing to the total liability for such non-economic loss.

217. At all times relevant to plaintiff's claims against Teva, Teva conformed its conduct to the state of medical knowledge, common and accepted procedures in the medical field, professional standards, and the medical and pharmacological state of the art.

218. Any alleged defect in metoclopramide could not have been detected or removed by a reasonable use of scientific procedures or techniques.

219. Plaintiff's breach of warranty claims are barred by plaintiff's failure to provide timely notice of any alleged breach of warranty.

220. Plaintiff's breach of warranty claims are barred by the absence of privity between plaintiff and Teva.

221. The First Amended Complaint fails to plead fraud with particularity, as required by Rule 9(b) of the Federal Rules of Civil Procedure.

222. The claims for relief based upon fraud and/or misrepresentation are barred, in whole or in part, because there were no misstatements or misrepresentations made by or attributable to Teva.

223. The claims for relief based upon fraud and/or misrepresentation are barred, in whole or in part, because at all relevant times the claimed

misrepresentations and/or omissions allegedly made by Teva, if any, were immaterial as a matter of law.

224. The claims for relief based upon fraud and/or misrepresentation are barred, in whole or in part, because at no time did plaintiff or her physicians rely upon any material misrepresentations or omissions by Teva.

225. The claims for relief based upon fraud and/or misrepresentation are barred, in whole or in part, because at no time did Teva have a duty to disclose allegedly omitted information as to the possible effects of long-term use of metoclopramide.

226. To the extent that plaintiff's claims sound in negligent misrepresentation, such claims are barred by the absence of privity between plaintiff and Teva.

227. Plaintiff has failed to join and include in this action all identifiable and indispensable parties without whom, in equity and fairness, this action should not proceed.

228. Plaintiff has failed to state a claim against Teva upon which relief may be granted for punitive or exemplary damages.

229. Any injuries, damages and/or losses allegedly sustained by plaintiff were caused in whole or in part by preexisting conditions, for which Teva bears no legal responsibility or liability.

230. Teva discharged its duty to warn by including fair and adequate warnings as to the risks, precautions and potential adverse reactions from using

its metoclopramide products in the product labeling therefor. Accordingly, Teva is not liable to plaintiff by virtue of the learned intermediary doctrine.

231. Plaintiff's claim for punitive damages is barred because an award of punitive damages would violate Teva's right to due process and equal protection.

WHEREFORE, Teva respectfully requests that the First Amended Complaint be dismissed as to it in all respects, together with such other and further relief as to this Court may seem just and proper.

Dated: Minneapolis, MN
March 13, 2008

FELHABER, LARSON, FENLON & VOGT PA

By: s/ David L. Hashmall
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Attorneys for Defendant Teva Pharmaceuticals USA, Inc.

UNITED STATES DISTRICT COURT
DISTRICT OF MINNESOTA

Case No. 0:07-cv-03919-DWF-XXX

[Filed March 13, 2008]

GLADYS MENSING	)
	)
Plaintiff	)
	)
v.	)
	)
WYETH, INC. et al.,	)
	)
Defendants.	)
	)

ANSWER OF UDL LABORATORIES, INC. TO PLAINTIFF'S FIRST AMENDED COMPLAINT

JURY TRIAL DEMANDED

Defendant UDL Laboratories, Inc. ("UDL"), by its attorneys, Felhaber, Larson, Fenlon & Vogt PA, as and for its Answer to the First Amended Complaint herein:

PRELIMINARY STATEMENT

Many of the paragraphs of the First Amended Complaint and of the individual allegations contained therein are addressed jointly to UDL and the other "Defendants," as that term is defined in the First Amended Complaint, or without distinction between them. UDL and the other Defendants are unrelated corporate entities. In general, UDL has no knowledge,

actual, constructive or otherwise, as to actions, conduct, business practices or corporate behavior of the other Defendants. Accordingly, in the responses that follow, UDL responds solely on its own behalf, and denies knowledge or information as to the truth or falsity of any and all allegations as to the other Defendants, except insofar as expressly averred otherwise.

UDL responds to the individual paragraphs of the First Amended Complaint as follows:

1. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 1 of the First Amended Complaint.

2. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 2 of the First Amended Complaint, except denies each and every such allegation insofar as it is alleged or implied that plaintiff was injured or otherwise suffered any damages as a result of any culpable conduct of UDL.

3. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 3 of the First Amended Complaint.

4. In response to paragraph 4 of the First Amended Complaint, admits that references in the First Amended Complaint to "Wyeth" may include individually and collectively all divisions and/or subsidiaries, Wyeth as successor in interest to A.H.

Robins, Inc., American Home Drugs Corporation, and ESI.

5. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 5 of the First Amended Complaint.

6. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 6 of the First Amended Complaint, except admits upon information and belief that metoclopramide manufactured by Wyeth was sold with an ESI Lederle, Inc. label.

7. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 7 of the First Amended Complaint.

8. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 8 of the First Amended Complaint.

9. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 9 of the First Amended Complaint.

10. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 10 of the First Amended Complaint.

11. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 11 of the First Amended Complaint.

12. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 12 of the First Amended Complaint.

13. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 13 of the First Amended Complaint.

14. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 14 of the First Amended Complaint.

15. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 15 of the First Amended Complaint.

16. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 16 of the First Amended Complaint.

17. Admits each and every allegation contained in paragraph 17 of the First Amended Complaint.

18. Denies each and every allegation contained in paragraph 18 of the First Amended Complaint, except admits that, from time to time, UDL has sold in

interstate commerce a generic form of metoclopramide for human use, including for use in the State of Minnesota, and that UDL's registered agent is Illinois Corporation Service.

19. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 19 of the First Amended Complaint.

20. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 20 of the First Amended Complaint.

21. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 21 of the First Amended Complaint.

22. In response to paragraph 22 of the First Amended Complaint, admits that Defendants are sometimes referred to collectively in the First Amended Complaint as the "Defendants."

23. Neither admits nor denies the allegations contained in paragraph 23 of the First Amended Complaint to the extent that they purport to state conclusions of law, except admits that UDL is a corporation and necessarily acts through its officers and employees.

24. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 24 of the First Amended Complaint, except admits that, from time to

time, UDL has sold in interstate commerce a generic form of metoclopramide for human use, including for use in the State of Minnesota.

25. Denies each and every allegation contained in paragraph 25 of the First Amended Complaint, except admits that, from time to time, UDL has sold in interstate commerce a generic form of metoclopramide for human use, including for use in the State of Minnesota, and further neither admits nor denies the allegations contained in paragraph 25 of the First Amended Complaint to the extent that they purport to state conclusions of law.

26. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 26 of the First Amended Complaint.

27. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 27 of the First Amended Complaint.

28. Admits upon information and belief each and every allegation contained in paragraph 28 of the First Amended Complaint.

29. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 29 of the First Amended Complaint.

30. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the

allegations contained in paragraph 30 of the First Amended Complaint.

31. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 31 of the First Amended Complaint.

32. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 32 of the First Amended Complaint.

33. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 33 of the First Amended Complaint, except denies that plaintiff used metoclopramide in accordance with its recommended directions for use.

34. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 34 of the First Amended Complaint, except denies each and every allegation insofar as it is alleged or implied that any injuries or damages suffered by plaintiff resulted from culpable conduct of UDL.

35. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 35 of the First Amended Complaint, except denies each and every allegation insofar as it is alleged or implied that any injuries or damages suffered by plaintiff resulted from culpable conduct of UDL.

36. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 36 of the First Amended Complaint.

37. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 37 of the First Amended Complaint.

38. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 38 of the First Amended Complaint, except denies each and every such allegation insofar as it is alleged or implied that any injuries or damages suffered by plaintiff resulted from culpable conduct of UDL.

39. Denies each and every allegation contained in paragraph 39 of the First Amended Complaint.

40. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 40 of the First Amended Complaint, except denies each and every allegation insofar as it is alleged or implied that any injuries or damages suffered by plaintiff resulted from culpable conduct of UDL.

41. Denies each and every allegation contained in paragraph 41 of the First Amended Complaint, except admits that the allegations in paragraph 41 of the First Amended Complaint purport to state plaintiff's contentions in this lawsuit.

42. Denies each and every allegation contained in paragraph 42 of the First Amended Complaint, except admits that, from time to time, UDL has sold in interstate commerce a generic form of metoclopramide for human use, including for use in the State of Minnesota.

43. Denies each and every allegation contained in paragraph 43 of the First Amended Complaint, except admits that metoclopramide is indicated for use as specified in its product labeling as approved from time to time by the FDA, and respectfully refers the Court to the labeling in force during the period of the plaintiff's alleged ingestion of metoclopramide for the terms thereof.

44. Denies each and every allegation contained in paragraph 44 of the First Amended Complaint, except admits that metoclopramide is indicated for use as specified in its product labeling as approved from time to time by the FDA, and respectfully refers the Court to the labeling in force during the period of the plaintiff's alleged ingestion of metoclopramide for the terms thereof.

45. Denies each and every allegation contained in paragraph 45 of the First Amended Complaint, except admits that the risk of developing tardive dyskinesia as a result of the use of metoclopramide may increase with the duration of treatment and total cumulative dose.

46. Denies each and every allegation contained in paragraph 46 of the First Amended Complaint, except admits that the use of metoclopramide can result in adverse reactions that may include, *inter alia*,

central nervous system disorders, depression with suicidal ideation, akathesia, tardive dyskinesia, acute dystonia, and visual disturbances.

47. Denies each and every allegation contained in paragraph 47 of the First Amended Complaint, except admits that the risk of experiencing certain adverse reactions to the use of metoclopramide, including tardive dyskinesia, may be related to the duration of treatment and total cumulative dose.

48. Denies each and every allegation contained in paragraph 48 of the First Amended Complaint, except admits that the risk of experiencing certain adverse reactions to the use of metoclopramide, including tardive dyskinesia, may be related to the duration of treatment and total cumulative dose, and that diabetes may be a co-risk factor thereto.

49. Denies each and every allegation contained in paragraph 49 of the First Amended Complaint, except admits that tardive dyskinesia is a disorder typically involving involuntary movements of the facial muscles and tongue.

50. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 50 of the First Amended Complaint.

51. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 51 of the First Amended Complaint.

52. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 52 of the First Amended Complaint, except admits upon information and belief that A.H. Robins Company, Inc. was the first to obtain approval from the FDA of an NDA for metoclopramide, which it sold in the United States under the brand name Reglan®.

53. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 53 of the First Amended Complaint.

54. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 54 of the First Amended Complaint.

55. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 55 of the First Amended Complaint.

56. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 56 of the First Amended Complaint.

57. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 57 of the First Amended Complaint, except admits upon information and belief that metoclopramide manufactured by Wyeth was sold with an ESI Lederle, Inc. label.

58. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 58 of the First Amended Complaint, except admits upon information and belief that as the holder of the NDA for Reglan®, the reference listed drug ("RLD") for UDL's metoclopramide products, Wyeth had such obligations to test, monitor and disclose information relating to the safety and efficacy of Reglan® as were imposed by and applicable from time to time under the U.S. Food, Drug and Cosmetic Act and the FDA's implementing regulations thereof.

59. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 59 of the First Amended Complaint.

60. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 60 of the First Amended Complaint, except admits upon information and belief that Wyeth prepared and disseminated full prescribing information for Reglan®, in the form, inter alia, of a package insert, in accordance with its FDA regulatory obligations, and caused such full prescribing information to be published from time to time in the PDR.

61. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 61 of the First Amended Complaint, except admits upon information and belief that the NDA for Reglan® was transferred from Wyeth to Schwarz.

62. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 62 of the First Amended Complaint, except admits upon information and belief that the NDA for Reglan® was transferred from Wyeth to Schwarz.

63. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 63 of the First Amended Complaint, except denies that UDL's metoclopramide products were defective or otherwise accompanied by inadequate warnings.

64. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 64 of the First Amended Complaint, except admits upon information and belief that Schwarz is currently listed as the holder of the NDA for Reglan®, the RLD for UDL's metoclopramide products.

65. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 65 of the First Amended Complaint, except admits upon information and belief that Schwarz is currently listed as the holder of the NDA for Reglan®, the RLD for UDL's metoclopramide products.

66. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 66 of the First Amended Complaint, except admits that Wyeth's and Schwarz's labeling of Reglan® disclosed that various

extrapyramidal symptoms and other adverse reactions may be associated with the use of metoclopramide.

67. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 67 of the First Amended Complaint, except admits upon information and belief that as a holders of the NDA for Reglan®, Wyeth and Schwarz had such obligations to test, monitor and disclose information relating to the safety and efficacy of Reglan® as were imposed by and applicable from time to time under the U.S. Food, Drug and Cosmetic Act and the FDA's implementing regulations thereof.

68. Denies each and every allegation contained in paragraph 68 of the First Amended Complaint, except denies knowledge or information as to whether Wyeth, Schwarz, or their predecessors made any false or fraudulent allegations regarding Reglan®.

69. Denies each and every allegation contained in paragraph 69 of the First Amended Complaint, except denies knowledge or information as to whether Wyeth, Schwarz, or their predecessors made any false or fraudulent allegations regarding Reglan®.

70. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 70 of the First Amended Complaint, except denies each and every such allegation insofar as it is alleged or implied that any injuries or damages suffered by plaintiff resulted from culpable conduct of UDL.

71. Denies each and every allegation contained in paragraph 71 of the First Amended Complaint, except denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations as to what Wyeth and Schwarz had actual knowledge of .

72. Denies each and every allegation contained in paragraph 72 of the First Amended Complaint, except denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations as to what Wyeth and Schwarz had actual knowledge of.

73. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 73 of the First Amended Complaint, except denies each and every such allegation insofar as it is alleged or implied that any injuries or damages suffered by plaintiff resulted from culpable conduct of UDL.

74. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 74 of the First Amended Complaint, except denies that UDL's metoclopramide products were defective or otherwise accompanied by inadequate warnings.

75. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 75 of the First Amended Complaint, except denies that UDL's metoclopramide products were defective or otherwise accompanied by inadequate warnings.

76. Admits upon information and belief each and every allegation contained in paragraph 76 of the First Amended Complaint.

77. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 77 of the First Amended Complaint, except neither admits nor denies the allegations contained in paragraph 77 of the First Amended Complaint to the extent that they purport to state conclusions of law.

78. Denies each and every allegation contained in paragraph 78 of the First Amended Complaint, except admits that, pursuant to applicable federal statutory law and FDA regulations, UDL's package insert for its metoclopramide products is required to be, and has at all relevant times been, identical to the package insert for Reglan®, its "reference-listed drug," in the form in which the same was approved from time to time by the FDA, except for permissible differences as enumerated in 21 C.F.R. § 314.94.

79. Denies each and every allegation contained in paragraph 79 of the First Amended Complaint.

80. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 80 of the First Amended Complaint, except admits upon information and belief that, when seeking prescribing information for a drug, doctors commonly refer to the labeling, in the form of the package insert or PDR entry, for the "brand name" or reference listed drug product.

81. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 81 of the First Amended Complaint, except admits upon information and belief that, when seeking prescribing information for a drug, doctors commonly refer to the labeling, in the form of the package insert or PDR entry, for the "brand name" or reference listed drug product.

82. Denies that UDL held an ANDA for metoclopramide at any time, and therefore denies each and every allegation contained in paragraph 82 of the First Amended Complaint.

83. Denies each and every allegation contained in paragraph 83 of the First Amended Complaint, except admits that the U.S. Food, Drug and Cosmetic Act and implementing FDA regulations thereunder applicable to drugs manufactured and/or sold pursuant to the ANDA process require that product labeling for such drugs conform at all times to the label for the pertinent reference listed drug, except for enumerated permissible differences.

84. Denies that UDL held an ANDA for metoclopramide at any time, and therefore denies each and every allegation contained in paragraph 84 of the First Amended Complaint, except admits that UDL had such obligations with respect to post-marketing safety surveillance of the drug as may have been imposed upon and applicable from time to time to distributors of prescription drugs pursuant to the U.S. Food, Drug and Cosmetic Act and the FDA's implementing regulations thereof.

85. Denies that UDL held an ANDA for metoclopramide at any time, and therefore denies each and every allegation contained in paragraph 85 of the First Amended Complaint, except admits that UDL had such obligations with respect to post-marketing safety surveillance of the drug as may have been imposed upon and applicable from time to time to distributors of prescription drugs pursuant to the U.S. Food, Drug and Cosmetic Act and the FDA's implementing regulations thereof.

86. Denies each and every allegation contained in paragraph 86 of the First Amended Complaint, except admits that pursuant to applicable Food and Drug Administration regulations UDL was not required to and did not independently verify the safety and efficacy of metoclopramide for its FDA-approved indications.

87. Denies each and every allegation contained in paragraph 87 of the First Amended Complaint, except admits that applicable Food and Drug Administration regulations and accepted industry practice did not require UDL to conduct systematic reviews of relevant medical literature.

88. Denies each and every allegation contained in paragraph 88 of the First Amended Complaint, except admits that applicable Food and Drug Administration regulations as well as FDA standard practices contemplated that the manufacturer of the reference-listed drug would conduct systematic literature searches and report relevant medical literature to the FDA.

89. Denies each and every allegation contained in paragraph 89 of the First Amended Complaint, except admits that if the FDA directs the NDA holder to amend its label, the ANDA holder is required to conform its label to the amended label for the reference listed drug.

90. Denies each and every allegation contained in paragraph 90 of the First Amended Complaint.

91. Denies each and every allegation contained in paragraph 91 of the First Amended Complaint, except admits that every shipping unit of UDL metoclopramide was accompanied by informational labeling, in the form of the package insert as approved from time to time by the FDA.

92. Denies each and every allegation contained in paragraph 92 of the First Amended Complaint.

93. Denies each and every allegation contained in paragraph 93 of the First Amended Complaint.

94. Denies each and every allegation contained in paragraph 94 of the First Amended Complaint, except admits that it had an obligation to distribute and sell its metoclopramide products in accordance with all applicable FDA regulations and provisions of the Food, Drug & Cosmetic Act.

95. Denies each and every allegation contained in paragraph 95 of the First Amended Complaint, except admits that, as specified in the product labeling, as approved from time to time by the FDA, UDL's metoclopramide products were indicated for the treatment of GERD and diabetic gastroparesis.

96. Denies each and every allegation contained in paragraph 96 of the First Amended Complaint.

97. Denies each and every allegation contained in paragraph 97 of the First Amended Complaint.

98. Denies each and every allegation contained in paragraph 98 of the First Amended Complaint.

99. Denies each and every allegation contained in paragraph 99 of the First Amended Complaint.

100. Denies each and every allegation contained in paragraph 100 of the First Amended Complaint.

101. Denies each and every allegation contained in paragraph 101 of the First Amended Complaint.

102. Denies each and every allegation contained in paragraph 102 of the First Amended Complaint.

103. Denies each and every allegation contained in paragraph 103 of the First Amended Complaint.

104. Denies each and every allegation contained in paragraph 104 of the First Amended Complaint.

105. Denies each and every allegation contained in paragraph 105 of the First Amended Complaint.

106. In response to paragraph 106 of the First Amended Complaint, repeats and realleges each and every response to paragraphs 1 through 105 of the First Amended Complaint as though hereinafter fully set forth at length.

107. Denies each and every allegation contained in paragraph 107 of the First Amended Complaint.

108. Denies each and every allegation contained in paragraph 108 of the First Amended Complaint, except admits that, if plaintiff ingested metoclopramide sold by UDL, she was expected to ingest it in the same form in which it was manufactured and shipped, but denies knowledge or information as to whether she did so.

109. Denies each and every allegation contained in paragraph 109 of the First Amended Complaint.

110. Denies each and every allegation contained in paragraph 110 of the First Amended Complaint.

111. Denies each and every allegation contained in paragraph 111 of the First Amended Complaint.

112. Denies each and every allegation contained in paragraph 112 of the First Amended Complaint.

113. Denies each and every allegation contained in paragraph 113 of the First Amended Complaint.

114. Denies each and every allegation contained in paragraph 114 of the First Amended Complaint.

115. Denies each and every allegation contained in paragraph 115 of the First Amended Complaint.

116. In response to paragraph 116 of the First Amended Complaint, repeats and realleges each and every response to paragraphs 1 through 115 of the

First Amended Complaint as though hereinafter fully set forth at length.

117. Denies each and every allegation contained in paragraph 117 of the First Amended Complaint.

118. Denies each and every allegation contained in paragraph 118 of the First Amended Complaint, except denies knowledge or information as to what plaintiff or her physicians relied upon.

119. Denies each and every allegation contained in paragraph 119 of the First Amended Complaint.

120. Denies each and every allegation contained in paragraph 120 of the First Amended Complaint.

121. Denies each and every allegation contained in paragraph 121 of the First Amended Complaint.

122. In response to paragraph 122 of the First Amended Complaint, repeats and realleges each and every response to paragraphs 1 through 121 of the First Amended Complaint as though hereinafter fully set forth at length.

123. Denies each and every allegation contained in paragraph 123 of the First Amended Complaint, except admits that, from time to time, UDL has sold a generic form of metoclopramide for human use, admits that, as specified in the product labeling as approved from time to time by the FDA, UDL's metoclopramide products were indicated for the treatment of GERD and diabetic gastroparesis, and further admits that UDL's metoclopramide products were safe and

effective for use in accordance with their FDA-approved indications and directions for use.

124. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 124 of the First Amended Complaint, except denies each and every such allegation insofar as it is alleged or implied that any injuries or damages suffered by plaintiff resulted from culpable conduct of UDL.

125. Denies each and every allegation contained in paragraph 125 of the First Amended Complaint.

126. Denies each and every allegation contained in paragraph 126 of the First Amended Complaint.

127. Denies each and every allegation contained in paragraph 127 of the First Amended Complaint.

128. Denies each and every allegation contained in paragraph 128 of the First Amended Complaint.

129. In response to paragraph 129 of the First Amended Complaint, repeats and realleges each and every response to paragraphs 1 through 128 of the First Amended Complaint as though hereinafter fully set forth at length.

130. Denies each and every allegation contained in paragraph 130 of the First Amended Complaint, except admits that it had an obligation to distribute and sell its metoclopramide products in accordance with all applicable FDA regulations and provisions of the Food, Drug & Cosmetic Act.

131. Denies each and every allegation contained in paragraph 131 of the First Amended Complaint.

132. Denies each and every allegation contained in paragraph 132 of the First Amended Complaint.

133. Denies each and every allegation contained in paragraph 133 of the First Amended Complaint.

134. Denies each and every allegation contained in paragraph 134 of the First Amended Complaint.

135. In response to paragraph 135 of the First Amended Complaint, repeats and realleges each and every response to paragraphs 1 through 134 of the First Amended Complaint as though hereinafter fully set forth at length.

136. Denies each and every allegation contained in paragraph 136 of the First Amended Complaint.

137. Denies each and every allegation contained in paragraph 137 of the First Amended Complaint.

138. Denies each and every allegation contained in paragraph 138 of the First Amended Complaint.

139. Denies each and every allegation contained in paragraph 139 of the First Amended Complaint.

140. Denies each and every allegation contained in paragraph 140 of the First Amended Complaint.

141. Denies each and every allegation contained in paragraph 141 of the First Amended Complaint.

142. Denies each and every allegation contained in paragraph 142 of the First Amended Complaint.

143. Denies each and every allegation contained in paragraph 143 of the First Amended Complaint.

144. Denies each and every allegation contained in paragraph 144 of the First Amended Complaint.

145. Denies each and every allegation contained in paragraph 145 of the First Amended Complaint.

146. Denies each and every allegation contained in paragraph 146 of the First Amended Complaint.

147. Denies each and every allegation contained in paragraph 147 of the First Amended Complaint.

148. In response to paragraph 148 of the First Amended Complaint, repeats and realleges each and every response to paragraphs 1 through 147 of the First Amended Complaint as though hereinafter fully set forth at length.

149. Denies each and every allegation contained in paragraph 149 of the First Amended Complaint.

150. Denies each and every allegation contained in paragraph 150 of the First Amended Complaint.

151. Denies each and every allegation contained in paragraph 151 of the First Amended Complaint.

152. Denies each and every allegation contained in paragraph 152 of the First Amended Complaint.

153. Denies each and every allegation contained in paragraph 153 of the First Amended Complaint.

154. In response to paragraph 154 of the First Amended Complaint, repeats and realleges each and every response to paragraphs 1 through 153 of the First Amended Complaint as though hereinafter fully set forth at length.

155. Denies each and every allegation contained in paragraph 155 of the First Amended Complaint.

156. Denies each and every allegation contained in paragraph 156 of the First Amended Complaint.

157. Denies each and every allegation contained in paragraph 157 of the First Amended Complaint.

158. Denies each and every allegation contained in paragraph 158 of the First Amended Complaint.

159. Denies each and every allegation contained in paragraph 159 of the First Amended Complaint.

160. Denies each and every allegation contained in paragraph 160 of the First Amended Complaint.

161. Denies each and every allegation contained in paragraph 161 of the First Amended Complaint.

162. Denies each and every allegation contained in paragraph 162 of the First Amended Complaint.

163. Denies each and every allegation contained in paragraph 163 of the First Amended Complaint.

164. In response to paragraph 164 of the First Amended Complaint, repeats and realleges each and every response to paragraphs 1 through 163 of the First Amended Complaint as though hereinafter fully set forth at length.

165. Denies each and every allegation contained in paragraph 165 of the First Amended Complaint.

166. Denies each and every allegation contained in paragraph 166 of the First Amended Complaint.

167. Denies each and every allegation contained in paragraph 167 of the First Amended Complaint.

168. Denies each and every allegation contained in paragraph 168 of the First Amended Complaint.

169. Denies each and every allegation contained in paragraph 169 of the First Amended Complaint.

170. In response to paragraph 170 of the First Amended Complaint, repeats and realleges each and every response to paragraphs 1 through 169 of the First Amended Complaint as though hereinafter fully set forth at length.

171. Denies each and every allegation contained in paragraph 171 of the First Amended Complaint.

172. Denies each and every allegation contained in paragraph 172 of the First Amended Complaint.

173. Denies each and every allegation contained in paragraph 173 of the First Amended Complaint.

174. Denies each and every allegation contained in paragraph 174 of the First Amended Complaint.

175. Denies each and every allegation contained in paragraph 175 of the First Amended Complaint.

176. In response to paragraph 176 of the First Amended Complaint, repeats and realleges each and every response to paragraphs 1 through 175 of the First Amended Complaint as though hereinafter fully set forth at length.

177. Denies each and every allegation contained in paragraph 177 of the First Amended Complaint.

178. Denies each and every allegation contained in paragraph 178 of the First Amended Complaint.

179. Denies each and every allegation contained in paragraph 179 of the First Amended Complaint.

180. In response to paragraph 180 of the First Amended Complaint, repeats and realleges each and every response to paragraphs 1 through 179 of the First Amended Complaint as though hereinafter fully set forth at length.

181. Denies each and every allegation contained in paragraph 181 of the First Amended Complaint.

182. Denies each and every allegation contained in paragraph 182 of the First Amended Complaint.

183. Denies each and every allegation contained in paragraph 183 of the First Amended Complaint.

184. Denies each and every allegation contained in paragraph 184 of the First Amended Complaint.

185. In response to paragraph 185 of the First Amended Complaint, repeats and realleges each and every response to paragraphs 1 through 184 of the First Amended Complaint as though hereinafter fully set forth at length.

186. Denies each and every allegation contained in paragraph 186 of the First Amended Complaint.

187. Denies each and every allegation contained in paragraph 187 of the First Amended Complaint, except admits that UDL had such obligations with respect to post-marketing safety surveillance of the drug as may have been imposed upon and applicable from time to time to distributors of prescription drugs pursuant to the U.S. Food, Drug and Cosmetic Act and the FDA's implementing regulations thereof.

188. Denies each and every allegation contained in paragraph 188 of the First Amended Complaint, except admits that UDL had such obligations with respect to post-marketing safety surveillance of the drug as may have been imposed upon and applicable from time to time to distributors of prescription drugs pursuant to the U.S. Food, Drug and Cosmetic Act and the FDA's implementing regulations thereof.

189. Denies each and every allegation contained in paragraph 189 of the First Amended Complaint.

190. Denies each and every allegation contained in paragraph 190 of the First Amended Complaint.

191. Denies each and every allegation contained in paragraph 191 of the First Amended Complaint.

192. In response to paragraph 192 of the First Amended Complaint, repeats and realleges each and every response to paragraphs 1 through 191 of the First Amended Complaint as though hereinafter fully set forth at length.

193. Denies each and every allegation contained in paragraph 193 of the First Amended Complaint.

194. Denies each and every allegation contained in paragraph 194 of the First Amended Complaint.

195. Denies knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 195 of the First Amended Complaint, except denies each and every allegation insofar as it is alleged or implied that any injuries or damages suffered by plaintiff resulted from culpable conduct of UDL.

196. Denies each and every allegation contained in paragraph 196 of the First Amended Complaint.

197. Denies each and every allegation contained in paragraph 197 of the First Amended Complaint.

198. In response to paragraph 198 of the First Amended Complaint, repeats and realleges each and every response to paragraphs 1 through 197 of the First Amended Complaint as though hereinafter fully set forth at length.

199. Denies each and every allegation contained in paragraph 199 of the First Amended Complaint.

200. Denies each and every allegation contained in paragraph 200 of the First Amended Complaint.

201. Denies each and every allegation contained in paragraph 201 of the First Amended Complaint.

202. Denies each and every allegation contained in paragraph 202 of the First Amended Complaint.

203. In response to paragraph 203 of the First Amended Complaint, admits that plaintiff seeks recovery for damages as alleged therein, but denies that UDL has any liability to plaintiff therefor.

AS AND FOR AFFIRMATIVE DEFENSES

204. Plaintiff's First Amended Complaint, and each and every allegation therein directed to UDL, fails to state a claim against UDL upon which relief may be granted.

205. Plaintiff's claims are barred in whole or in part by the applicable statutes of limitations.

206. Plaintiff's claims against UDL are barred by laches, waiver, and/or estoppel.

207. If plaintiff sustained any injury or incurred any loss or damage as alleged in the First Amended Complaint, the same resulted in whole or in part from an intervening cause and/or causes, and any action on the part of UDL was not the proximate and/or

competent producing cause of plaintiff's alleged injuries.

208. If plaintiff sustained any injury or incurred any loss or damages as alleged in the First Amended Complaint, the same were caused in whole or in part by acts or omissions of another or others over whom UDL neither exercised nor had any right of control, for which UDL is and was not responsible, and whose conduct UDL had no duty or reason to anticipate or control.

209. If in fact the First Amended Complaint is held to contain a claim upon which relief may be granted, then plaintiff's recovery, if any, should be reduced by the relative amount of comparative fault attributable to plaintiff or her agents or persons other than UDL.

210. The manufacture, marketing and labeling of metoclopramide was controlled by federal law and UDL was at all times in compliance with applicable federal law with respect thereto; therefore, the First Amended Complaint fails to state a claim upon which relief may be granted in that, inter alia, such causes of action, if upheld, would impede, impair, frustrate or burden the effectiveness of federal law regulating the field of prescription items and would constitute an invalid burden by this court on interstate commerce, and would, therefore, violate the Supremacy Clause (Article VI, Section 2) and the Commerce Clause (Article I, Section 8) of the United States Constitution.

211. In the event plaintiff is found to have suffered any injury, disease, damage, pain and/or disability, the degree of responsibility, negligence, and

fault of each person who contributed to said injuries should be determined, and UDL should be held liable only for that proportion of the resulting damage which corresponds to its degree of fault, responsibility, or negligence, if any.

212. Any damages, injuries or losses that may have been sustained by plaintiff as alleged in the First Amended Complaint were sustained only after plaintiff knowingly and voluntarily assumed any alleged risk inherent in the use of metoclopramide.

213. Plaintiff failed to heed the warnings provided by UDL.

214. UDL is not a proper party.

215. Upon information and belief, any injury, loss or damage that plaintiff may have sustained was caused in whole or in part by plaintiff's own negligence.

216. If UDL is found liable to plaintiff for any non-economic loss allegedly suffered by plaintiff, such liability equals fifty percent or less of the total liability of all persons liable, and the aggregate liability of such other persons equals or exceeds fifty percent of the total liability. Accordingly, UDL's liability, if any, to plaintiff for plaintiff's non-economic loss shall not exceed UDL's equitable share determined in accordance with the relative culpability of each person causing or contributing to the total liability for such non-economic loss.

217. At all times relevant to plaintiff's claims against UDL, UDL conformed its conduct to the state

of medical knowledge, common and accepted procedures in the medical field, professional standards, and the medical and pharmacological state of the art.

218. Any alleged defect in metoclopramide could not have been detected or removed by a reasonable use of scientific procedures or techniques.

219. Plaintiff's breach of warranty claims are barred by plaintiff's failure to provide timely notice of any alleged breach of warranty.

220. Plaintiff's breach of warranty claims are barred by the absence of privity between plaintiff and UDL.

221. The First Amended Complaint fails to plead fraud with particularity, as required by Rule 9(b) of the Federal Rules of Civil Procedure.

222. The claims for relief based upon fraud and/or misrepresentation are barred, in whole or in part, because there were no misstatements or misrepresentations made by or attributable to UDL.

223. The claims for relief based upon fraud and/or misrepresentation are barred, in whole or in part, because at all relevant times the claimed misrepresentations and/or omissions allegedly made by UDL, if any, were immaterial as a matter of law.

224. The claims for relief based upon fraud and/or misrepresentation are barred, in whole or in part, because at no time did plaintiff or her physicians rely upon any material misrepresentations or omissions by UDL.

225. The claims for relief based upon fraud and/or misrepresentation are barred, in whole or in part, because at no time did UDL have a duty to disclose allegedly omitted information as to the possible effects of long-term use of metoclopramide.

226. To the extent that plaintiff's claims sound in negligent misrepresentation, such claims are barred by the absence of privity between plaintiff and UDL.

227. Plaintiff has failed to join and include in this action all identifiable and indispensable parties without whom, in equity and fairness, this action should not proceed.

228. Plaintiff has failed to state a claim against UDL upon which relief may be granted for punitive or exemplary damages.

229. Any injuries, damages and/or losses allegedly sustained by plaintiff were caused in whole or in part by preexisting conditions, for which UDL bears no legal responsibility or liability.

230. UDL discharged its duty to warn by including fair and adequate warnings as to the risks, precautions and potential adverse reactions from using its metoclopramide product in the product labeling therefor. Accordingly, UDL is not liable to plaintiff by virtue of the learned intermediary doctrine.

231. Plaintiff's claim for punitive damages is barred because an award of punitive damages would violate UDL's right to due process and equal protection.

WHEREFORE, UDL respectfully requests that the First Amended Complaint be dismissed as to it in all respects, together with such other and further relief as to this Court may seem just and proper.

Dated: Minneapolis, MN
March 13, 2008

FELHABER, LARSON, FENLON & VOGT PA

By: s/ David L. Hashmall
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Attorneys for Defendant
UDL Laboratories, Inc.

UNITED STATES DISTRICT COURT
DISTRICT OF MINNESOTA

Civil No. 07-3919 (DWF/SRN)

[Filed June 17, 2008]

Gladys Mensing,

Plaintiff,

v.

WYETH, INC. (d/b/a WYETH); SCHWARZ PHARMA, INC.; PLIVA, Inc.; TEVA PHARMACEUTICALS, USA, INC.; ALPHARMA, INC., d/b/a ALPHARMA PHARMACEUTICALS; UDL LABORATORIES, INC.; ACTAVIS ELIZABETH, LLC; and PUREPAC PHARMACEUTICAL CO.; and the following fictitious party defendants (whether singular or plural, individual or corporate): No. 1, that entity which originally obtained permission from the U.S. Food and Drug Administration to market the drug branded Reglan; No. 2, that entity which obtained permission from the FDA to market the Reglan, metoclopramide and/or metoclopramide HCI ingested by Gladys Mensing; No. 3, that entity which originally manufactured and sold any Reglan which was ultimately ingested by Gladys Mensing; No. 4, that entity which originally manufactured and sold any Reglan, metoclopramide and/or metoclopramide HCI which was ultimately ingested by Gladys

Mensing: No. 5, that entity which marketed Reglan or generic metoclopramide and/or metoclopramide HCI, jointly and individually,

Defendants.

MEMORANDUM OPINION AND ORDER

Daniel J. McGlynn, Esq., and Patty F. Trantham, Esq., McGlynn, Glisson & Koch, APLC; and Lucia J. W. McLaren, Esq., and Michael K. Johnson, Esq., Goldenberg & Johnson, PLLC, counsel for Plaintiffs.

Bridget M. Ahmann, Esq., and Erin M. Verneris, Esq., Faegre & Benson LLP; and Jeffrey R. Pilkington, Esq., and Tom Wagner, Esq., Davis, Graham & Stubbs, LLP, counsel for Defendant Wyeth, Inc.

Andrew J. Calica, Esq., and Henninger S. Bullock, Esq., Mayer Brown, LLP; and Erin M. Verneris, Esq., and Bridget M. Ahmann, Esq., Faegre & Benson LLP, counsel for Defendant Schwartz Pharma, Inc.

Joseph P. Thomas, Esq., Matthew V. Brammer, Esq., Rex A. Littrell , Esq., and Tiffany Reece Clark, Esq., Ulmer & Berne LLP; and Jan R. McLean, Esq., Tracy J. Van Steenburgh, Esq., and Dana M. Lenahan, Esq., Halleland Lewis Nilan & Johnson PA, counsel for Defendants PLIVA, Inc.

David L. Hashmall, Esq., Fellhaber Larson Fenlon & Vogt, PA, counsel for Defendants Teva Pharmaceuticals USA, Inc. and UDL Laboratories, Inc.

Bradley J. Linderman, Esq., and Michael D. Hutchens, Esq., Meagher & Geer, PLLP; and Richard A. Dean, Esq., Tucker Ellis & West, counsel for Defendants Alpharma Inc., Actavis Elizabeth, LLC, and Purepac Pharmaceutical Co.

INTRODUCTION

This matter is before the Court on a Motion to Dismiss brought by Actavis Elizabeth, LLC ("Actavis"); a Motion to Dismiss or for Summary Judgment brought by Pliva, Inc. ("Pliva"); and a Motion for Relief Under Fed. R. Civ. P. 56(f) brought by Plaintiff Gladys Mensing. For the reasons stated below, the Court grants Actavis's and Pliva's motions and denies Plaintiff's motion.[1]

BACKGROUND

In her Amended Complaint, Plaintiff alleges that on or about March 23, 2001, her physician prescribed the drug Reglan to her to treat diabetic gastroparesis. (Am. Compl. ¶ 27). The active ingredient in Reglan is metoclopramide ("MCP"). MCO, which is available in brand (Reglan) or generic form, is used to treat certain gastrointestinal disorders. Plaintiff alleges that she ingested Reglan/MCP from March 23, 2001, until March 2005, and that her long-term ingestion of Reglan/MCP caused her to develop tardive dyskinesia,

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[1] The question presented by both Actavis's and Pliva's motions to dismiss is purely legal in nature. Accordingly, further factual discovery is unnecessary and Plaintiff's motion under Fed. R. Civ. P. 56(f) is denied.

a neurological movement disorder. (*Id.* ¶¶ 27, 32, 34, 37, 38.)

Both Actavis and Pliva manufacture MCP, a generic version bioequivalent of Reglan.[2] Reglan, the reference listed drug for MCP, was approved by the FDA in 1980. In March 1985, the FDA required that Reglan's label be updated to include a warning regarding the risk of developing tardive dyskinesia. Actavis and Pliva revised their insert labeling to comport to approved changes to the Reglan label. There is no dispute that the labels for both Actavis's and Pliva's MCP were at all relevant times the same as Wyeth's Reglan label.

Plaintiff asserts state-law tort claims against both Wyeth and the manufacturers of generic MCP. Although Plaintiff has asserted a variety of claims against Actavis and Pliva, at the core of all of Plaintiff's claims is the basic assertion that Actavis and Pliva failed to adequately warn about the association between long-term ingestion of MCP and movement disorders. For example, Plaintiff alleges that Actavis and Pliva ignored scientific and medical literature establishing a higher risk of developing tardive dyskinesia, failed to request a labeling revision to the FDA, and failed to report safety information directly to the medical community.

Actavis and Pliva move separately to dismiss Plaintiffs claims against them, arguing that Plaintiff's claims are preempted by federal law.

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[2] Defendant Wyeth, Inc., is the name brand manufacturer of Reglan.

DISCUSSION

I. Motions to Dismiss

A. Standard of Review

In deciding a motion to dismiss, a court assumes all facts in the complaint to be true and construes all reasonable inferences from those facts in the light most favorable to the complainant. *Morton v. Becker*, 793 F.2d 185, 187 (8th Cir. 1986). In doing so, however, a court need not accept as true wholly conclusory allegations, *Hanten v. Sch. Dist. of Riverview Gardens*, 183 F.3d 799, 805 (8th Cir. 1999), or legal conclusions drawn by the pleader from the facts alleged. *Westcott v. City of Omaha*, 901 F.2d 1486, 1488 (8th Cir. 1990). A court may consider the complaint, matters of public record, orders, materials embraced by the complaint, and exhibits attached to the complaint in deciding a motion to dismiss under Rule 12(b)(6) of the Federal Rules of Civil Procedure. *Porous Media Corp. v. Pall Corp.*, 186 F.3d 1077, 1079 (8th Cir. 1999).

To survive a motion to dismiss, a complaint must contain "enough facts to state a claim to relief that is plausible on its face." *Bell Atl. Corp. v. Twombly*, 127 S. Ct. 1955, 1974 (2007). Although a complaint need not contain "detailed factual allegations," it must contain facts with enough specificity "to raise a right to relief above the speculative level." *Id.* at 1964-65. This standard "calls for enough fact[s] to raise a reasonable expectation that discovery will reveal evidence of [the claim]." *Id.* at 1965. The Court evaluates a motion brought under Rule 12(c) under the same standard as a motion brought under Rule 12(b)(6). Fed. R. Civ. P. 12(c) and (h)(2).

B. Federal Preemption

A state law that conflicts with a federal law is preempted under the Supremacy Clause of the Constitution, U.S. Const. art. VI, cl. 2. *Hillsborough County, Fla. v. Automated Med. Labs., Inc.*, 471 U.S. 707, 712-13 (1985). Congressional intent to preempt state law can either be expressed in statutory language or implied in the structure and purpose of federal law. *Id.* Implied preemption has two types–field and conflict preemption. Field preemption is inferred where Congress legislates so pervasively in a particular field that no room remains for supplementary state legislation. *Id.* Even if Congress has not completely displaced state regulation, preemption may occur when state law actually conflicts with federal law. *Id.* Conflict preemption arises when compliance with both federal and state regulations is a physical impossibility, or when state law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress. *Id.* (citing *Florida Lime & Avocado Growers, Inc. v. Paul*, 373 U.S. 132, 142-43 (1963) and *Hines v. Davidowitz*, 312 U.S. 52, 67 (1941)). State laws can be pre-empted by both federal statutes and federal regulations. *Id.* at 713.

Both Actavis and Pliva assert that Plaintiff's claims are conflict preempted. First, they argue that as generic drug manufacturers, they cannot comply with both federal law that requires their generic drug labels to be the "same as" the Reglan® label and with a state-imposed duty to heighten warning labels. In particular, Actavis and Pliva contend that it would be impossible for it to comply with both the Abbreviated New Drug Application ("ANDA") provisions of the Food, Drug & Cosmetic Act ("FDCA") and the labeling requirements

Plaintiff seeks to impose pursuant to state law. In addition, both Actavis and Pliva maintain that Plaintiff's claims are conflict preempted because the state laws pose an obstacle to Congressional objectives in enacting federal law applicable to generic drug manufacturers and vesting exclusive authority to regulate prescription drug labeling with the Food and Drug Administration ("FDA").

In support of their preemption arguments, both Actavis and Pliva point to the Drug Price Competition and Patent Term Restoration Act of 1984 (the "Hatch-Waxman Act" or the "Act") (codified at 21 U.S.A. § 355(j)). The Hatch-Waxman Act codified the ANDA procedures being used by the FDA. Actavis and Pliva assert that under the ANDA procedures, a generic manufacturer is required to put exactly the same language on its warning labels as the listed drug.[3]

1. Regulatory Framework

To determine whether or not Plaintiff's claims are preempted, the Court must first understand the relevant regulatory framework. The FDA is the federal agency charged by Congress in the FDCA with regulating the manufacture, sale, and labeling of new prescription drug products that are marketed for human consumption and, in particular, to ensure the safety and efficacy of new drugs. 21 U.S.C. § 393. In this capacity, the FDA regulates the introduction of all new drugs. 21 U.S.C. § 355(b). Under 21 U.S.C.

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[3] Despite the fact that the bases for Actavis's and Pliva's preemption arguments vary to some degree, the Court analyzes their motions to dismiss together.

§ 355(a) "[n]o person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) of this section is effective with respect to such drug." Section 355(b) applies to "pioneer" or "innovator" drugs. A manufacturer seeking approval to market a pioneer drug must submit a New Drug Application ("NDA"). 21 U.S.C. § 355(b). As part of the NDA, the manufacturer must submit, among other things, "full reports of investigations" on the drug's safety and effectiveness and "specimens of the labeling proposed to be used" for the new drug. 21 U.S.C. § 355(b)(1)(A)-(F). The FDA may refuse an application if it finds that the investigations "do not include adequate tests ... to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof." 21 U.S.C. § 355(d)(1).

In 1984, Congress amended the FDCA by passing the Hatch-Waxman Act. The legislative history of the Hatch-Waxman Act reveals that the primary purpose of amending the FDCA to implement the ANDA procedure was to increase the availability of low cost generic drugs by establishing a generic drug approval procedure. (*See* Aff. of Tiffany Reece Clark ("Clark Aff.") ¶¶ 2 & 3, Exs. A & B.) The FDCA, as amended, provides for an ANDA procedure that allows for the expedited FDA approval of a generic version of a drug previously approved under the FDA (a "listed drug").[4] *See* 21 U.S.C. § 355(j); *see also Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241 (Fed. Cir. 2000)

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[4] A "listed drug" refers to a drug previously approved that serves as the basis for a generic drug. 21 C.F.R. § 314.3.

(explaining the ANDA process).[5] 21 U.S.C. § 355(j) applies to generic drugs, or drugs that are based on another previously FDA approved or "listed" drug. When a drug for which approval is sought is the "same as a listed drug," then an applicant may submit an abbreviated application complying with the ANDA provisions of 21 C.F.R. § 314.94. 21 U.S.C. § 355(j)(1); 21 C.F.R. § 314.92(a). The manufacturer of a generic drug must show that the generic drug has the same active ingredients and is the "bioequivalent" of the listed drug. 21 U.S.C. § 355(j)(2)(A)(ii) and (iv). In addition, an applicant filing an ANDA must submit:

> information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug . . . except for changes required because of differences approved under a petition filed under subparagraph (C) or because the new drug and the listed drug are produced or distributed by different manufacturers

21 U.S.C. § 355(j)(2)(A)(v) (emphasis added). To this effect, an ANDA applicant must submit a side-by-side comparison of the applicant's proposed labeling. 21 C.F.R. § 314.94(a)(8)(iv). The labeling for the proposed drug "must be the same as the labeling approved for the reference listed drug," with the exception of certain

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[5] Prior to the Hatch-Waxman Act, the FDA created an ANDA procedure for the approval of "duplicate" drug products. Those procedures were codified by the Hatch-Waxman Act. *See* 57 Fed. Reg. at 17951 (Apr. 28, 1992) (explaining that the Act adopted, with few modifications, the FDA's ANDA procedure for pre-1962 drugs).

allowable changes. *Id.* These allowable changes may include:

> ... differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act.

Id.

The FDA will not approve an ANDA if information submitted by the applicant is "insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug." 21 C.F.R. § 314.127(a)(7). Moreover, the FDA may withdraw approval of a generic drug if the labeling for the generic product varies from that of the listed drug. 21 C.F.R. § 314.150(b)(10).

2. Plaintiff's Claims

With this framework in mind, the Court must determine whether Plaintiff's claims against Actavis and Pliva conflict with the FDCA or the FDA regulations, so as to be preempted by the federal law. As a threshold matter, Plaintiff argues that there is a strong presumption against preemption. The Supreme Court has stated:

> In all pre-emption cases, and particularly in those in which Congress has legislated in a field which the States have traditionally occupied, we start with the assumption that the historic

> police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress.

Medtronic, Inc. v. Lohr, 518 U.S. 470, 485 (1996) (quotations omitted). Although commonly acknowledged, the presumption against preemption is not always appropriate. *See Buckman Co. v. Plaintiff's Legal Comm.*, 531 U.S. 341, 347-48 (2001). In the context of conflict preemption, which analyzes preemption in the absence of explicit Congressional intent, "the lack of a Congressional directive expressly approving or rejecting preemption in the context of drug labeling regulations is not determinative." *See Colacicco v. Apotex Inc.*, 521 F.3d 253, 265 & n.11 (3d Cir. 2008). Thus, the Court must analyze the propriety of preemption where Congress has not explicitly expressed its intent.

Plaintiff alleges that Actavis and Pliva's MCP labels failed to adequately warn of the risk or prevalence of tardive dyskinesia. In particular, Plaintiff claims that the risk ratio of developing tardive dyskinesia was significantly higher than the ratio listed on the Reglan and MCP labels.[6] Actavis and Pliva argue that these failure to warn claims are preempted because they, as generic manufacturers, could not unilaterally alter their labels to include a warning that varied from that of the listed drug, Reglan. In addition, Actavis and Pliva argue that

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[6] This allegation is at the heart of all of Plaintiff's claims against Actavis and Pliva. Thus, all of Plaintiff's claims are essentially "failure to warn" claims and are encompassed by the Court's preemption analysis.

Plaintiff's failure to warn claims are preempted because they stand as an obstacle to the accomplishment of the full purposes and objectives of the FDCA, the Hatch-Waxman Act, and the corresponding regulatory scheme.

Plaintiff asserts that her state law claims do not present a conflict because compliance with both state and federal regulations is possible and that Actavis and Pliva could have provided stronger warnings about the risks posed by prolonged exposure to MCP without conflicting with FDA regulations. In particular, Plaintiff argues that Actavis and Pliva could have altered their labeling to strengthen warnings without prior approval of the FDA; sought FDA approval for such a change; or provided health care professionals with stronger warnings by other means, such as a "Dear Doctor" letter. The Court addresses each argument in turn.

The Court first turns to Plaintiff's argument that Actavis and Pliva can, and are required to, strengthen their product warnings without prior FDA approval. After reviewing the statutory provisions of the Act, the legislative history of the Act, the Act's governing regulations, and comments made by the FDA[7], the

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[7] When Congress has not unambiguously expressed its intent as to a particular question of statutory interpretation, the Court will defer to the agency's answer on the issue if it is based on a permissible construction of the statute. *Chevron, U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837, 842-43 (1984). Here, the FDA's position on the ability of a generic manufacturer to unilaterally alter its label is based on a permissible construction of the relevant federal statutes and

Court concludes that a generic drug manufacturer may not unilaterally strengthen a label without prior approval of the FDA.

Under the statutory provisions of the Act, there is no dispute that Actavis's and Pliva's MCP labels were required to be "the same as the labeling approved" for Reglan when the initial ANDA applications were submitted. 21 U.S.C. § 355(j)(2)(A)(v). Plaintiff argues, however, that 21 U.S.C. § 355 (j)(2)(A)(v) does *not* apply to post-approval labeling. Instead, Plaintiff argues that the FDA regulations require both name brand and generic manufacturers to strengthen warning labels post-approval. The Court disagrees.

The FDA's own comments in implementing the Hatch-Waxman Act support the conclusion that a generic manufacturer is not free to unilaterally alter the labeling from that of the name brand drug. In particular, in a proposed rule implementing the Act, the FDA described various types of labeling differences that the FDA might consider acceptable under the statute's permitted exceptions. *See* 54 Fed. Reg. 28872 at 28884 (July 10, 1989). Notably, the FDA emphasized limited exceptions to the requirement that a generic drug label be the "same as" that of the listed drug. *Id.* The FDA stated that "[t]he agency will not accept ANDA's for products with significant changes in labeling (such as new warnings or precautions) intended to address newly introduced safety or effectiveness problems not presented by the listed drug." *Id.*

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promulgating regulations. Accordingly, that position is entitled to deference.

In addition, under the statutory scheme, the FDA may withdraw an ANDA if the ANDA drug labeling "is no longer consistent with that for the listed drug." 21 C.F.R. § 314.150(b)(10). In this regard, the FDA has explained:

> Because an ANDA must have labeling that is the same as the reference listed drug ..., FDA believes that a generic drug product approved on the basis of studies conducted on the listed drug and whose labeling is inconsistent with the listed drug's labeling might not be considered safe and effective for use under the conditions prescribed, suggested, or recommended in the listed drug's labeling. FDA, therefore, has revised § 314.150 to permit the agency to withdraw approval of an ANDA if the applicant fails to maintain labeling in compliance with the requirements of the act.

57 Fed. Reg. 17950 at 17961 (Apr. 28, 1992) (emphasis added).

Several FDA responses to comments submitted in connection with proposed ANDA regulations underscore the notion that the ANDA drug's label must remain the same as that of the listed drug. For example, in response to a comment proposing that ANDA labeling provisions be "revised to permit ANDA applicants to deviate from the labeling for the reference listed drug to add contraindications, warnings, precautions, adverse reactions and other safety-related information," the FDA stated:

> FDA disagrees with the comment[]. Except for labeling differences due to exclusivity of a

> patent and differences under section 505(j)(2)(v) of the act, the ANDA's product labeling must be the same as the listed drug product's labeling because the listed drug product is the basis for ANDA approval. Consistent labeling will assure physicians, health professionals, and consumers that a generic drug is as safe and effective as its brand-name counterpart. (See 54 FR 28872 at 28884.) If an ANDA applicant believes new safety information should be added to a product's labeling, it should contact FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised. After approval of an ANDA, if an ANDA holder believes that new safety information should be added, it should provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised.

Id. at 17961 (emphasis added). In addition, in response to a comment recommending that the "FDA accept ANDAs with warnings or precautions in addition to those on the reference listed drug's label, provided that such information was not indicative of diminished safety or effectiveness of the generic product," the FDA stated:

> As for accepting ANDA's with additional warnings or precautions, section 505(j)(2)(A)(v) and (j)(3)(G) of the act requires that the applicant's proposed labeling be the same as that of the reference listed drug unless: (1) The labeling differences are due to an approved petition under section 505(j)(2)(C) of the act (otherwise referred to as a "suitability petition");

> or (2) the drug product and the reference listed drug are produced or distributed by different manufacturers. Thus, the exceptions in section 505(j)(2)(A)(v) of the act are limited. In addition, under the patent and exclusivity provisions of the act, the ANDA labeling may be required to carry fewer indications than the reference listed product's labeling or to have other labeling differences. In the preamble to the proposed rule, the agency described various types of labeling differences that might fall within the permitted exceptions.

Id. at 17953 (citations omitted).

Further, in industry guidance documents, the FDA reiterates the ANDA labeling requirements. For example, in its Guidance for Industry regarding Changes to an Approved NDA or ANDA, the FDA states:

> A drug product labeling change includes changes in the package insert, package labeling, or container label. An applicant should promptly revise all promotional labeling and drug advertising to make it consistent with any labeling change implemented in accordance with the regulations. <u>All labeling changes for ANDA products must be consistent with section 505(j) of the Act [codified at 21 U.S.C. § 355(j)]</u>.

(Clark Aff. ¶ 15, Ex. N. at 20 (emphasis added).) Again, section 505(j) (codified at 21 U.S.C. § 355(j)) requires that the labeling be the "same as" the listed drug.

That a generic drug manufacturer cannot unilaterally change the label is also supported by the positions of the FDA provided in recent *amicus briefs*. For example, in an *amicus brief* filed in *Colacicco v. Apotex, Inc.*, 521 F.3d 253 (3d Cir. 2008), the FDA asserted the following:

> For a generic drug manufacturer, there is no statutory or regulatory provision permitting a labeling change to be made without prior FDA approval. To the contrary, a generic drug manufacturer is required to conform to the approved labeling for the listed drug. If a generic drug manufacturer believes that new safety information should be added to the label for its drug, it is directed to contact FDA with "adequate supporting information." 57 Fed. Reg. at 17,961. The agency will consider this information and determine whether the labeling for both the generic drug and the innovator drug should be revised. *Id.*

(Clark Aff. ¶ 19, Ex. Q at 7-8.)[8]

Plaintiff relies primarily on 21 C.F.R. § 314.70(c), the "Changes Being Effected" ("CBE") regulation, for the proposition that generic drug manufacturers can change their product labels without waiting for FDA approval.[9] Section 314.70(c) allows NDA manu-

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[8] The Third Circuit recognized that the "FDA states that generic drug manufacturers may not add new warnings to the approved labeling for the listed drug." *Colacicco*, 521 F.3d at 260 n.5.

[9] With the Court's permission, Pliva submitted a copy of an *amicus brief* filed by the United States in a case currently before

facturers, under certain limited circumstances, to strengthen warnings prior to FDA approval. The FDA has explained, however, that the CBE provision does *not* permit ANDA manufacturers to make unilateral changes. In particular, the FDA explained:

> The plaintiff asserts that 21 C.F.R. § 314.70(c) empowers a generic drug manufacturer to add a new warning to the label for its drug without prior FDA approval. That regulatory provision, however—like the other provisions of Title 21, Part 314, Subpart B of the Code of Federal Regulations—applies to applications involving drug products for which a full application has been submitted, *i.e.*, innovator drug products. Drug manufacturers that submit abbreviated applications to market generic drugs are subject to the requirements set forth in Title 21, Part 314, Subpart C. Although Subpart C contains a provision requiring applicants to "comply with the requirements of §§ 314.70 and 314.71 regarding the submission of supplemental applications and other changes to an approved abbreviated application," 21 C.F.R. § 317.97, that provision does not modify the requirement that the drug label for a generic drug must be the same as the label for the approved innovator

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the United States Supreme Court. Pliva contends that portions of the argument therein would be helpful to the Court, particularly with respect to the interpretation of § 314.70(c). Plaintiff has moved to strike Pliva's submission. The Court denies Plaintiff's motion. While the Court reviewed Pliva's submission and the attached *amicus brief*, this review did not alter the Court's analysis or the outcome of the dispositive motions before the Court.

> drug (with limited exceptions not relevant here). Any ambiguity in the regulatory text has been clarified by FDA, which explained at the time of promulgation that the regulations do not authorize drug manufacturers to add new warnings to the approved labeling for the innovator drug. *See* 57 Fed. Reg. at 17,961, 17,953, 17,955.

(Clark Aff. ¶ 18, Ex. Q at 8 n.4 (emphasis added).) In addition, in a rule proposed on January 2008, the FDA confirmed that § 314.70 does not permit unilateral label changes by ANDA manufacturers. *See* 73 Fed. Reg. 2848 at 2848-49 (Jan. 16, 2008). In particular, the FDA stated: "FDA is proposing to amend its regulations regarding changes to an approved NDA, BLA, or PMA to codify the agency's longstanding view on when a change to the labeling of an approved drug, biologic, or medical device may be made in advance of the agency's review." *Id.* at 2849. In the Supplementary Information section of the proposed rule, the FDA explains: "CBE changes are not available for generic drugs approved under an [ANDA] application under 21 U.S.C. 355(j). To the contrary, a generic drug manufacturer is required to conform to the approved labeling for the listed drug." *Id.* at 2849 n.1 (citations omitted).

The Court concludes that under the federal statutory scheme, the labeling for generic drugs must always remain the "same as" that of the name brand drug and that a generic drug manufacturer cannot unilaterally change its label without prior FDA approval. Here, it is undisputed that at all relevant times, Actavis's and Pliva's MCP drug labels were the same as that of the listed drug Reglan. Plaintiff's

failure to warn claims against Actavis and Pliva rely on state law imposing a duty on the generic drug manufacturers to provide adequate warnings that Actavis and Pliva allegedly did not provide. Any such duty to unilaterally heighten their warning labels, however, would directly conflict with the federal law requiring that their labels be the "same as" those of the listed drug, Reglan. Indeed, under these circumstances, it would be impossible for Actavis and Pliva to abide by both state and federal laws. If Plaintiff's claims were not preempted, Actavis and Pliva would be forced to choose between complying with the federal law while being exposed to state tort liability, or unilaterally adding a heightened warning to their labels at the risk of exposing themselves to federal liability. This conflict would stand as an obstacle to the accomplishment and full purposes and objectives of the Hatch-Waxman Act, a key purpose of which is to increase the availability of low-cost generic drugs and to relax the generic approval and labeling process.

The Court turns next to Plaintiff's argument that Actavis and Pliva could have sought to strengthen their warnings through the prior approval supplemental process under 21 C.F.R. § 314.70. Based on the statutory scheme discussed above, the Court discerns no legal duty requiring a generic drug manufacturer to propose revised labeling. While the manufacturer of a generic drug may seek to add safety information to a drug label, in order to do so, it must first provide certain information to the FDA; the FDA then in turn determines whether the labeling for both the generic and listed drug should be revised. *See* 57 Fed. Reg. 17950 at 17961 cmt. 40. The outcome of any such request to make a revision is uncertain and would

require speculation as to what the FDA might have done. In light of the statutory scheme discussed in detail above, the Court determines that Plaintiff's failure to warn claims, insofar as they assert that Actavis and Pliva had an independent duty to seek to add safety information to MCP's label, again would directly conflict with the statutory scheme of the Hatch-Waxman Act and would stand as an obstacle to the accomplishment and execution of the full purposes and objectives of the Act.

Finally, the Court turns to Plaintiff's argument that Actavis and Pliva were free to employ other means to warn health care professionals, such as submitting a "Dear Doctor" letter. The regulatory scheme, however, does not allow for ANDA manufacturers to send "Dear Doctor" letters. Instead, for drugs approved through the ANDA procedures, "the Secretary shall undertake any communication plan to health care providers required under [the risk evaluation and mitigation strategies][10] for the applicable drug." 21 U.S.C. § 355-1(i)(2)(A). The imposition of an independent duty on the part of the generic manufacture to send "Dear Doctor" letters would directly conflict with the statutory scheme of the Hatch-Waxman Act. In addition, this Court's speculation over what the FDA might have done if Actavis or Pliva had requested such a letter would stand as an obstacle to the accomplishment and execution of the full purposes and objectives of the Act.

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[10] This includes sending letters to health care providers. 21 U.S.C. § 355-1(e)(3)(A).

CONCLUSION

Accordingly, **IT IS HEREBY ORDERED** that:

1. Actavis's Motion to Dismiss (Doc. No. 39) is **GRANTED**.

2. Pliva's Motion to Dismiss (Doc. No. 64) is **GRANTED**.

3. Plaintiff's Rule 56(f) Motion is **DENIED.**

4. Plaintiff's Motion to Strike (Doc. No. 85) is **DENIED.**

5. This action is dismissed as to Defendants Actavis and Pliva.

Dated: June 17, 2008

s/Donovan W. Frank
DONOVAN W. FRANK
Judge of United States
District Court

UNITED STATES DISTRICT COURT
DISTRICT OF MINNESOTA

Civil No. 07-3919 (DWF/SRN)

[Filed October 30, 2008]

Gladys Mensing,

Plaintiff,

v.

WYETH, INC. (d/b/a WYETH); SCHWARZ PHARMA, INC.; TEVA PHARMACEUTICALS, USA, INC.; UDL LABORATORIES, INC.; and the following fictitious party defendants (whether singular or plural, individual or corporate): No. 1, that entity which originally obtained permission from the U.S. Food and Drug Administration to market the drug branded Reglan; No. 2, that entity which obtained permission from the FDA to market the Reglan, metoclopramide and/or metoclopramide HCl ingested by Gladys Mensing; No. 3, that entity which originally manufactured and sold any Reglan which was ultimately ingested by Gladys Mensing; No. 4, that entity which originally manufactured and sold any Reglan, metoclopramide and/or metoclopramide HCl which was ultimately ingested by Gladys Mensing; No. 5, that entity which marketed Reglan or generic metoclopramide

and/or metoclopramide HCl, jointly and individually,

Defendants.

AMENDED MEMORANDUM OPINION AND ORDER

Daniel J. McGlynn, Esq., and Patty F. Trantham, Esq., McGlynn, Glisson & Koch, APLC; and Lucia J. W. McLaren, Esq., and Michael K. Johnson, Esq., Goldenberg & Johnson, PLLC, counsel for Plaintiffs.

Bridget M. Ahmann, Esq., and Erin M. Verneris, Esq., Faegre & Benson LLP; and Jeffrey R. Pilkington, Esq., and Tom Wagner, Esq., Davis, Graham & Stubbs, LLP, counsel for Defendant Wyeth, Inc.

Andrew J. Calica, Esq., and Henninger S. Bullock, Esq., Mayer Brown, LLP; and Erin M. Verneris, Esq., and Bridget M. Ahmann, Esq., Faegre & Benson LLP, counsel for Defendant Schwartz Pharma, Inc.

David L. Hashmall, Esq., and Donald G. Heeman, Esq., Feihaber Larson Fenton & Vogt, PA, counsel for Defendants Teva Pharmaceuticals USA, Inc. and UDL Laboratories, Inc.

The Court amends the Memorandum, Opinion and Order dated October 24, 2008, so as to make a correction in footnote 8. The footnote is amended to indicate that Schwarz, not Wyeth, cited to the cases listed in footnote 8.

INTRODUCTION

This matter is before the Court on a Motion for Summary Judgment brought by Schwarz Pharma, Inc. ("Schwarz"); a Motion for Summary Judgment brought by Teva Pharmaceuticals USA, Inc. ("Teva") and UDL Laboratories, Inc. ("UDL"); and a Motion for Summary Judgment brought by Wyeth, Inc. ("Wyeth"). For the reasons stated below, the Court grants the pending motions.

BACKGROUND

In her Amended Complaint, Plaintiff[1] alleges that her physician prescribed the drug Reglan to her to treat diabetic gastroparesis. The active ingredient in Reglan is metoclopramide ("MCP"). MCP, which is available in name-brand form (Reglan) or generic form ("generic MCP"), is used to treat certain gastrointestinal disorders. Plaintiff alleges that the long-term ingestion of MCP caused her to develop tardive dyskinesia, a neurological movement disorder.

Plaintiff asserts state-law tort claims against Defendants as the manufacturers and distributors of Reglan and generic MCP. At the core of all of Plaintiff's claims is the basic assertion that Defendants failed to adequately warn about the association between long-term ingestion of MCP and movement disorders. In an Order dated June 17, 2008 (the "June 2008 Order"), the Court held that Plaintiff's claims against manufacturers of generic MCP, Actavis Elizabeth, LLC

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[1] The Court notes and respects that Plaintiff personally attended the recent hearings in this matter.

("Actavis") and Pliva, Inc. ("Pliva"), were preempted by federal law. In the June 2008 Order, the Court concluded that under the federal statutory scheme, the labeling for generic drugs must always remain the same as that of the name brand drug (in this case Reglan), and that a generic drug manufacturer cannot unilaterally change its label without prior approval from the Food and Drug Administration ("FDA"). The Court held that because Plaintiff's failure to warn claims relied on state law imposing a duty on the generic drug manufacturers, these claims directly conflicted with, and stood as an obstacle to the execution of, federal law.

Wyeth manufactured and distributed name-brand Reglan from approximately 1989 through 2001. (Aff. of Paul Minicozzi, Ph.D. ("Minicozzi Aff.") ¶ 3.) From approximately 1995 through 2001, Wyeth also manufactured and sold generic MCP through its subsidiaries. (Minicozzi Aff. ¶ 4.) In December 2001, Wyeth sold to Schwarz the rights to manufacture and distribute name-brand Reglan tablets. (Decl. of Jeff. Siefert ("Siefert Decl.") ¶¶ 1-2; Minicozzi Aff. ¶ 3.) Schwarz thereafter manufactured and distributed name-brand Reglan through 2005. At no time did Schwarz manufacture or distribute generic MCP. (Siefert Decl. ¶ 3.) Teva has manufactured and sold only generic MCP. (Aff. of Philip Erickson in Supp. of Mot. for Summ. J. ("Erickson Aff.") ¶ 2.) At times relevant to this matter, Teva and UDL were parties to a Supply and Distribution Agreement under which UDL distributed generic MCP manufactured by Teva. (Erickson Aff. ¶ 4; Affidavit of Timothy G. Wait in Supp. of Mot. for Summ. J. ("Wait Aff.") ¶ 2.)

Plaintiff's counsel provided pharmacy records reflecting Plaintiff's MCP purchases from November 15, 2001, through the present. (Decl. of Erin Verneris ("Verneris Decl.") ¶ 2, Ex. A.) Those records demonstrate that from November 2001 until the time Plaintiff stopped taking MCP, Plaintiff was dispensed only generic MCP products; none of the generic MCP was manufactured or distributed by Schwarz; and Plaintiff never purchased or used any name-brand Reglan manufactured by Wyeth.[2]

Here, in three separate motions, Teva, UDL, Wyeth, and Schwarz have moved for summary judgment on Plaintiff's claims against them.

DISCUSSION

I. Standard of Review

Summary judgment is proper if there are no disputed issues of material fact and the moving party is entitled to judgment as a matter of law. Fed. R. Civ. P. 56(c). The Court must view the evidence, and the inferences that may be reasonably drawn from the

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[2] The record reflects that the pharmacy records prior to November 2001 are not available due to the pharmacy's record-keeping policy. On July 10, 2008, Plaintiff sought and was granted leave to seek specific discovery to identify the manufacturers of MCP that supplied Plaintiff's pharmacy prior to 2001. (Doc. No. 94.) The additional discovery sought by Plaintiff would not affect the outcome of Schwarz's current motion, as Schwarz did not acquire the rights associated with name-brand Reglan until December 2001. In addition, even though the discovery sought could show that Wyeth supplied the pharmacy with name-brand Reglan, the discovery would be unable to provide evidence of what drugs were actually dispensed to Plaintiff.

evidence, in the light most favorable to the nonmoving party. *Enter. Bank v. Magna Bank of Mo.*, 92 F.3d 743, 747 (8th Cir. 1996). However, as the Supreme Court has stated, "[s]ummary judgment procedure is properly regarded not as a disfavored procedural shortcut, but rather as an integral part of the Federal Rules as a whole, which are designed 'to secure the just, speedy, and inexpensive determination of every action.'" *Celotex Corp. v. Catrett*, 477 U.S. 317, 327 (1986) (quoting Fed. R. Civ. P. 1).

The moving party bears the burden of showing that there is no genuine issue of material fact and that it is entitled to judgment as a matter of law. *Enter. Bank*, 92 F.3d at 747. The nonmoving party must demonstrate the existence of specific facts in the record that create a genuine issue for trial. *Krenik v. County of Le Sueur*, 47 F.3d 953, 957 (8th Cir. 1995). A party opposing a properly supported motion for summary judgment may not rest upon mere allegations or denials but must set forth specific facts showing that there is a genuine issue for trial. *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 256 (1986).

II. Generic Manufacturer Liability

Teva, UDL, and Wyeth (collectively, the "Generic MCP Defendants")[3] move to dismiss Plaintiff's claims

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[3] Despite the fact that there is no evidence that Plaintiff ingested any name-brand Reglan manufactured by Wyeth, Plaintiff claims that because Wyeth manufactures the name-brand drug, it, along with Schwarz, is liable for allegedly misstating the true risks associated with ingesting generic MCP. The Court discusses this assertion of "name-brand manufacturer liability" in Section III below.

against them. The Generic MCP Defendants assert that because they are manufacturers of generic MCP, Plaintiff's claims are preempted by federal law for the reasons set forth in the Court's June 2008 Order. Specifically, the Generic MCP Defendants contend that Plaintiff's claims against them are identical to the claims asserted against Actavis and Pliva that were determined to be preempted by federal law in the June 2008 Order. Plaintiff does not dispute that only generic MCP was dispensed to her. Further, Plaintiff does not attempt to distinguish between Actavis and Pliva and the Generic MCP Defendants with respect to the issue of federal preemption. At the time of the hearing, Plaintiff's only arguments in opposition to the Generic MCP Defendants' motions were those previously made in opposition to Actavis and Pliva's prior motions to dismiss. The Court has already heard, considered, and rejected these arguments. (Doc. No. 86.)

Moreover, because the issue of federal preemption as it relates to generic manufacturers of MCP has already been decided in this case, Plaintiff's opposition to the Generic MCP Defendants' present motions is akin to a request to file a motion to reconsider the June 2008 Order. Pursuant to Local Rule 7.1(g), a request for leave to file a motion for reconsideration will only be granted upon a showing of "compelling circumstances." A motion to reconsider should not be employed to relitigate old issues but to "afford an opportunity for relief in extraordinary circumstances." *Dale & Selby Superette & Deli v. U .S. Dept. of Agric.*, 838 F. Supp. 1346, 1348 (D. Minn. 1993).

After the hearing on this motion, Plaintiff submitted supplemental authority to the Court, in particular a recently filed opinion in *McKenney v.*

Purepac Pharmaceutical Co., F052606 Super. Ct. No. 343927 (Cal. 5th Dist. Ct. App. Sept. 25, 2008) (Aff. of Michael K. Johnson ("Johnson Aff.") ¶ 2, Ex. 1). In *McKenney*, a California Court of Appeal reversed the decision of a California Superior Court, wherein the lower court sustained the demurrer of a generic MCP manufacturer on preemption grounds. The California Court of Appeal held "that the federal requirement that a generic drug have the same labeling as a reference listed drug does not necessarily result in federal preemption of a state tort action against the generic manufacturer for failure to adequately warn of the dangers of the drug." *(Id.* at 2.) The Court has reviewed the *McKenney* opinion and determines that it would not alter the Court's analysis and conclusions set forth in the June 2008 Order. First, the decision is not binding on the Court. Second, the Court disagrees with the *McKenney* court's brief discussion of the FDA's regulatory scheme and its bearing on the preemption analysis. This Court previously considered and discussed the same regulatory scheme and came to the opposite conclusion on the issue of preemption. Because the issue of preemption was already considered and the *McKenney* case does not alter this Court's conclusions, the Court finds that no compelling circumstances exist to warrant a motion to reconsider the June 2008 Order.

Accordingly, Teva's and UDL's motion is granted; Wyeth's motion is granted on the issue of Wyeth's liability as a manufacturer of generic MCP.

III. Name-Brand Manufacturer Liability[4]

In December 2001, Schwarz acquired from Wyeth the rights to manufacture and distribute name-brand Reglan. (Siefert Decl. ¶¶ 1-3.) At no time did Schwarz manufacture or distribute generic MCP. (Siefert Decl. ¶ 3.) Plaintiff concedes that "it appears" that she never ingested name-brand Reglan manufactured by Schwarz or Wyeth. (Pl.'s Mem. in Opp. to Def. Schwarz Pharma Inc.'s Mot. for Summ. J. at 3.) Even so, Plaintiff maintains that Schwarz and Wyeth are liable for negligent misrepresentation, misrepresentation by omission, fraud by concealment, and constructive fraud for misstating the true risks associated with ingesting MCP.[5] Plaintiff asserts that she is pursuing only the above-mentioned claims and states that all of those claims are essentially contained within the elements of negligent misrepresentation.

The elements of negligent misrepresentation are: (1) a duty of reasonable care in conveying information; (2) breach of that duty by negligently giving false information; (3) reasonable reliance on the misrepresentations, which reliance is the proximate

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[4] Wyeth did not move separately on the issue of "name-brand liability," but joined Schwarz's motion at the hearing.

[5] In Count Ten of her Amended Complaint, Plaintiff asserts a claim for intentional infliction of emotional distress. Schwarz argues that this claim was time-barred. Plaintiff does not object to the entry of summary judgment based on the statute of limitations. Accordingly, Count Ten is dismissed.

cause of physical injury; and (4) damages.[6] *See Smith v. Brutger Cos.*, 569 N.W.2d 408, 414 (Minn. 1997). Here, the Court's focus is on whether Wyeth and Schwarz, as name-brand manufacturers, have a legal duty to warn so as to give rise to a claim by a consumer for injuries caused by the ingestion of another manufacturer's generic product.

Schwarz and Wyeth argue that they are entitled to summary judgment on Plaintiff's claims against them because they cannot be liable for injuries allegedly caused by another manufacturer's generic product. Plaintiff, on the other hand, asserts that Schwarz and Wyeth were under a legal duty to be truthful in their representations to the public about its name-brand products even if the aggrieved member of the public is not injured by those products.

The leading case on whether a name-brand manufacturer can be held liable for injuries caused by a generic equivalent is *Foster v. American Home Products Corp.*, 29 F.3d 165, 171 (4th Cir. 1994). In *Foster*, the parents of a child who died after being given the generic equivalent of one of Wyeth's brand name prescription drugs sued Wyeth for negligent misrepresentation.[7] 29 F.3d 165, 166-67. The plaintiffs

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[6] The tort of negligent misrepresentation involving the risk of physical harm has not been specifically adopted or rejected in Minnesota. *Smith*, 569 N.W.2d at 414.

[7] The *Foster* plaintiffs also sued Wyeth for negligence, strict liability, and breach of warranty. These causes of action were dismissed on summary judgment because Wyeth did not manufacture the drug ingested by the plaintiffs' child. *Foster*, 165

in the *Foster* case argued that the fact that Wyeth did not manufacture the drug their child ingested did not shield Wyeth from a negligent misrepresentation claim. *Id.* at 169. With respect to the plaintiffs' negligent misrepresentation claim, the United States Court of Appeals for the Fourth Circuit held that a name-brand manufacturer was under no duty to the consumers of another company's product and could not be held liable for injuries stemming from the ingestion of another generic manufacturer's product. *Id.* at 171. In so holding, the Fourth Circuit noted that "[t]here is no legal precedent for using a name brand manufacturer's statements about its own product as a basis for liability for injuries caused by other manufacturers' products, over whose production the name brand manufacturer had no control." *Id.* at 170. The Fourth Circuit also rejected the plaintiffs' arguments that it was foreseeable to Wyeth that misrepresentations as to its product could result in the injury to users of generic equivalents. *Id.* at 171. The Fourth Circuit explained that to impose such a duty in that case "would be to stretch the concept of foreseeability too far." *Id. Foster* has been adopted or cited with approval by numerous federal and state courts. *See, e.g., Colacicco v. Apotex, Inc.*, 432 F. Supp. 2d 514, 538-39, 540 (E.D. Pa. 2006), *aff'd* 521 F.3d 253 (3d Cir. 2008) (holding that "a name brand drug manufacturer does not owe a legal duty to consumers of a generic equivalent of its drug"; noting that *Foster*

F.3d at 167. At that time, the district court allowed plaintiffs' negligent misrepresentation claim to stand. *Id.*

has wide-spread acceptance).[8] The Court finds *Foster* persuasive.

More importantly, the law in Minnesota similarly provides that a party does not have a duty to warn about another manufacturer's product. *See Flynn v. Am. Home Prods. Corp.*, 627 N.W.2d 342, 350 (Minn. Ct. App. 2001). In *Flynn*, plaintiff brought an action against American Home Products Corporation ("AHPC"), the manufacturer of the name-brand version of "fen-phen," alleging that misrepresentations made by AHPC to the FDA caused her to ingest the generic equivalent of fen-phen, which then injured her.[9] *Id.* The plaintiff asserted claims for fraud, negligent misrepresentation, and violation of Minnesota consumer fraud statutes. *Id.* at 346. The Minnesota Court of Appeals affirmed the district court's grant of summary judgment in favor of AHPC, rejecting the plaintiff's theory of recovery.[10] As to whether AHPC had a duty to warn about the generic manufacturer's drug, the court explained that "[a]lthough federal

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[8] Indeed, Schwarz has cited to numerous cases involving generic MCP wherein the *Foster* case has been accepted and applied. *See, e.g., Sharp v. Leichus*, Case No. 2004-CA-0643, 2006 WL 515532, at *4 (Fla. Cir. Ct. Feb. 17, 2006), *aff'd* 925 So.2d 555 (Fla. App. 1 Dist. Jan. 22, 2007); *Smith v. Wyeth, Inc.*, No. 5:07-CV-18-R, 2008 WL 2677051, at *4 (W.D. Ky. June 30, 2008); *Pustejovsky v. Wyeth, Inc.*, No. 4:07-CV-103-Y, 2008 WL 1314902, at *2 (N.D. Tex. April 3, 2008); *Block v. Wyeth*, No. Civ. A 3-02-CV-1077, 2003 WL 203067, at *2 (N.D. Tex. Jan. 28, 2003).

[9] The court in *Flynn* analyzed plaintiff's claims under a "fraud-on-the-FDA" theory and under Minnesota common law. *Id.* at 350-51.

[10] The court in *Flynn* also held alternatively that the plaintiff's claims were preempted by federal law. *Id.* at 349.

regulations required respondents to disclose product safety information to the FDA, respondents did not owe appellant, who did not purchase their product and with whom they had no relationship, the same obligation." *Id.* at 350 (citing *In re Minn. Breast Implant Litig.*, 36 F. Supp. 2d 863, 880 (D. Minn. 1998)).

While *Flynn*, *Foster*, and numerous other cases have answered "no" to the question of duty under these circumstances, Plaintiff nonetheless asserts that the question deserves examination and that alleged inaccuracies in Wyeth's and Schwarz's warnings can form the basis of a claim for negligent misrepresentation to the extent that a generic drug manufacturer must or will foreseeably rely on those disclosures in formulating their own warnings. Plaintiff asserts that there are sound justifications for imposing such a duty–namely because the issuance of a name-brand manufacturer's label is analogous to a product endorsement and the Restatement (Second) Torts forms a basis for exacting such a duty. The Court disagrees. As a federal court sitting in diversity, the Court must apply Minnesota state law. *Erie R.R. Co. v. Tompkins*, 304 U.S. 64, 78 (1938). Under Minnesota law, as set forth in *Flynn*, Schwarz and Wyeth did not have a legal duty to warn Plaintiff so as to give rise to Plaintiff's claim for injuries caused by the ingestion of another manufacturer's generic MCP. *See Flynn*, 627 N.W.2d 342 at 350. The Court discerns no support under Minnesota law for the recognition of a cause of action against a manufacturer for representations concerning its own product based on an injury caused by another manufacturer's product. Accordingly, Plaintiff's negligent misrepresentation claim is dismissed.

The Court is sympathetic to the fact that Plaintiff may lack a legal remedy due to the fact that she did not ingest name-brand Reglan and that her claims against the generic manufacturers are preempted by federal law. However, such sympathy does not warrant a departure from clear Minnesota law. That Plaintiff is left without a remedy is an issue for the legislature, not this Court.

CONCLUSION

Accordingly, **IT IS HEREBY ORDERED that:**

1. Wyeth's Motion for Summary Judgment (Doc. No. 110) is **GRANTED.**

2. Teva and UDL's Motion for Summary Judgment (Doc. No. 87) is **GRANTED.**

3. Schwarz's Motion for Summary Judgment (Doc. No. 96) is **GRANTED.**

LET JUDGMENT BE ENTERED ACCORDINGLY.

Dated: October 30, 2008

s/Donovan W. Frank
DONOVAN W. FRANK
Judge of United States
District Court

United States Court of Appeals
For the Eighth Circuit

No. 08-3850

[Filed November 27, 2009]

Gladys Mensing,

Plaintiff - Appellant,

v.

Wyeth, Inc., doing business as Wyeth; Pliva, Inc.; Teva Pharmaceuticals, USA, Inc.; Alpharma, Inc., doing business as Alpharma Pharmaceuticals; UDL Laboratories, Inc.; Actavis Elizabeth, LLC; Schwarz Pharma, Inc ; Purepac Pharmaceutical Company, and the following fictitious party defendants (whether singular or plural, individual or corporate): No. 1, that entity which originally obtained permission from the U.S. Food and Drug Administration to market the drug branded Reglan No. 2, that entity which obtained permission from the FDA to market the Reglan, metoclopramide and/or metoclopramide HCl ingested by Gladys Mensing No. 3, that entity which originally manufactured and sold any Reglan which was ultimately ingested by Gladys Mensing No. 4, that entity which originally manufactured and sold any Reglan, metoclopramide and/or metoclopramide HCl which was ultimately ingested by Gladys Mensing No. 5, that entity which marketed

Reglan or generic metoclopramide and/or metoclopramide HCl, jointly and individually,

Defendants - Appellees

Appeal from the United States District Court for the District of Minnesota.

Submitted: October 20, 2009
Filed: November 27, 2009

Before: WOLLMAN, MURPHY, and BYE, Circuit Judges.

MURPHY, Circuit Judge.

Gladys Mensing brought this failure to warn and misrepresentation case against a number of manufacturers of Reglan and its generic form, alleging that the medication she had taken caused her to develop tardive dyskinesia, a severe neurological movement disorder. The manufacturers moved for summary judgment and dismissal. The district court dismissed her claims against the generic defendants on the basis of federal preemption and against the name brand manufacturers on the basis that she had not taken their products. Mensing appeals, and we affirm the judgment in favor of the name brand manufacturers but reverse as to the generic manufacturers.

I.

In March 2001 Gladys Mensing's doctor prescribed Reglan to treat her diabetic gastroparesis, and her pharmacist filled her prescription with its generic bioequivalent, metoclopramide. Minn. Stat. § 151.21. After four years of ingesting metoclopramide, Mensing developed tardive dyskinesia. Mensing sued the manufacturers and/or distributors of generic metoclopramide (generic defendants). Mensing's complaint includes a variety of claims, but she has not challenged the district court's characterization that "at the core" they all assert failure to warn. Mensing v. Wyeth, Inc., 562 F.Supp.2d 1056, 1058 (D.Minn. 2008). Mensing argues that despite mounting evidence that long term metoclopramide use carries a risk of tardive dyskinesia far greater than indicated on the label, no metoclopramide manufacturer took steps to change the label warnings. According to her allegations, metoclopramide manufacturers in fact promoted the drug for long term use. Although she never ingested the name brand drug, Mensing also sued the manufacturers of Reglan (name brand defendants) for fraud and negligent misrepresentation on the theory that her doctor relied on Reglan's label when assessing the risks and proper use of metoclopramide.

All defendants filed motions to dismiss or for summary judgment. The district court granted the motions to dismiss by generic defendants Actavis Elizabeth and Pliva and motions for summary judgment by generic defendants Teva, Wyeth, and UDL Laboratories on the ground of federal preemption. The court concluded that Mensing's failure to warn claims created an impermissible conflict with federal law because they would require generic manufacturers

to deviate from the name brand drug label; they were therefore preempted. The court also granted summary judgment to name brand defendants Schwarz and Wyeth,[1] holding that they owed Mensing no duty of care under Minnesota law because she never ingested their product.

Grants of motions to dismiss and for summary judgment are subject to de novo review. We affirm a dismissal if, taking all the plaintiff's allegations as true, they "state a claim to relief that is plausible on its face." Bell Atlantic Corp. v. Twombly, 550 U.S. 544, 570 (2007). On review of summary judgment, we "view the evidence in the light most favorable to the nonmoving party" and affirm only when "there are no genuine issues of material fact[.]" Takele v. Mayo Clinic, 576 F.3d 834, 838 (8th Cir. 2009) (quotations omitted).

II.

We first address the generic defendants' argument that federal law preempts state failure to warn claims against them. Since a purely legal issue of statutory interpretation is raised, the generic defendants' motions for summary judgment and dismissal will be considered together.

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[1] Wyeth manufactured both Reglan and generic metoclopramide. It joined in the summary judgment motions of both the generic and name brand defendants.

A.

All prescription drugs require approval by the Food and Drug Administration (FDA) before they may be marketed. Manufacturers of new drugs submit a new drug application (NDA) to the FDA. 21 U.S.C. § 355(a)-(b). An NDA must include information about the drug's safety and efficiency gleaned from clinical trials. Id. at §§ 355(b), (d). It must also propose a label reflecting appropriate use, warnings, precautions, and adverse reactions. 21 C.F.R. § 201.56.

Recognizing a need to bring more affordable generic drugs to market as quickly as possible after the patents of name brand drugs expire, Congress passed the Drug Price Competition and Patent Term Restoration Act in 1984. This statute amended the Food, Drug, and Cosmetic Act (FDCA) and is therefore referred to as the Hatch-Waxman Amendments to the FDCA. The Hatch-Waxman Amendments provided an abbreviated new drug application (ANDA) procedure for generic manufacturers. 21 U.S.C. § 355(j). Generic manufacturers do not need to repeat the clinical trials conducted by name brand manufacturers. ANDA's are approved based on the initial safety profile of the name brand drug, as well as any postmarketing surveillance. See Bartlett v. Mutual Pharmaceutical Co., Inc., --- F.Supp.2d ---, No. 08-cv-358-JL, 2009 WL 3126305, at *2-*6 (D.N.H. Sept. 30, 2009) (detailing requirements and history of ANDA procedure). As a result, ANDA applicants must show the FDA that their drug is essentially the same as the name brand drug and that their proposed label is in relevant part identical to the name brand drug label. 21 C.F.R. § 314.94(a)(8).

Drug labels are subject to change. New risks may become apparent only after the drug has been used more widely and for longer periods. When a manufacturer has "reasonable evidence of an association of a serious hazard with a drug[,]" the drug's label must be revised; "a causal relationship need not have been proved." 21 C.F.R. § 201.57(e) (redesignated as 21 C.F.R. § 201.80(e) in 2006, after the conduct at issue here). Manufacturers cannot distribute a "misbranded" drug, 21 U.S.C. §§ 331(a)-(b), including a drug whose "labeling is false or misleading in any particular." Id. at § 352(a). The FDA has several enforcement mechanisms to ensure that drugs with misleading labels are taken off the market. See, e.g., id. at § 333, 355(e).

There are several procedures in 21 C.F.R. § 314.70 by which a manufacturer may supplement its application and propose changes to the drug or its label. "Major changes" require the FDA's prior approval through a prior approval supplement. 21 C.F.R. § 314.70(b). Manufacturers may implement "moderate changes," including changing a label to strengthen a warning based on newly acquired information, through a Changes Being Effected (CBE) supplement. 21 C.F.R. § 314.70(c)(6)(iii)(A)-(D). Manufacturers may implement CBE changes before the FDA formally approves them.

The FDA approved Reglan in 1980. Manufacturers began seeking approval for generic versions of metoclopramide five years later. The generic metoclopramide labels have always been in relevant part the same as the Reglan label. The label warnings about tardive dyskinesia, and other similar but less severe extrapyramidal symptoms, did not change from

1985 through the time Mensing stopped ingesting the drug in 2005. Mensing alleges that despite mounting evidence that long term metoclopramide users were at a much greater risk of movement disorders than indicated by the drug's label, no manufacturer took any step to enhance the warnings.[2] Moreover, Mensing asserts that defendants promoted metoclopramide for long term use even though the FDA had approved the drug only for use up to 12 weeks.

Acting on its own initiative pursuant to the Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (FDAAA), the FDA ordered manufacturers of Reglan and generic metoclopramide on February 26, 2009 to add a boxed warning to their labels about the increased risks of tardive dyskinesia from long term metoclopramide usage.

B.

In considering a preemption defense we must be attuned to Congressional intent and the presumption against preemption. Wyeth v. Levine, 129 S.Ct. 1187, 1194-95 (2009) (quotation omitted) (courts must assume "that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress."). In Wyeth, the Supreme Court ruled that failure to warn claims against name brand manufacturers are not preempted by the FDCA. The Court noted the

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[2] Mensing notes that in July 2004 the FDA approved Schwarz's request to add a sentence to the Reglan label: "Therapy should not exceed 12 weeks in duration."

historic coexistence of state tort remedies and federal regulation of prescription drugs:

> If Congress thought state-law suits posed an obstacle to its objectives, it surely would have enacted an express pre-emption provision at some point during the FDCA's 70-year history. But despite its 1976 enactment of an express pre-emption provision for medical devices, . . . Congress has not enacted such a provision for prescription drugs. . . . Its silence on the issue, coupled with its certain awareness of the prevalence of state tort litigation, is powerful evidence that Congress did not intend FDA oversight to be the exclusive means of ensuring drug safety and effectiveness.

Id.

The Hatch-Waxman Amendments are part of this 70 year history and they do not explicitly preempt suits against generic manufacturers. Congress could have crafted a preemption provision for generic drugs in its 1984 amendments, having done so for medical devices less than 10 years earlier. It chose not to do that. Seven in ten prescriptions filled in this country are now for generic drugs. Susan Okie, Multinational Medicines-Ensuring Drug Quality in an Era of Global Manufacturing, 361 New Eng. J. Med. 737, 738 (2009). After Wyeth, we must view with a questioning mind the generic defendants' argument that Congress silently intended to grant the manufacturers of most prescription drugs blanket immunity from state tort liability when they market inadequately labeled products.

The generic defendants distinguish Wyeth on the ground that it concerned claims against brand name manufacturers, but the decision carries important implications for their situation as well. See, e.g., Wyeth, 129 S. Ct. at 1197-98 ("[I]t has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. It is charged both with crafting an adequate label and with ensuring that its warnings remain adequate[.]"). The district court did not have the teachings of Wyeth available when it rendered its decision, but courts which have subsequently considered this issue have almost uniformly ruled that tort claims against generic manufacturers are not preempted. See, e.g., Stacel v. Teva Pharmaceuticals, USA, 620 F.Supp.2d 899, 906-907 (N.D. Ill. 2009); Schrock v. Wyeth, 601 F.Supp.2d 1262, 1265-66 (W.D. Okla. 2009). The Fourth Circuit reached the same conclusion much earlier in considering whether a plaintiff injured by a generic drug can hold a name brand manufacturer liable. Foster v. American Home Products Corp., 29 F.3d 165, 170 (4th Cir. 1994) ("The statutory scheme governing premarketing approval for drugs simply does not evidence Congressional intent to insulate generic drug manufacturers from liability for misrepresentations made regarding their products, or to otherwise alter state products liability law.").

Even when a federal law does not expressly preempt state law claims, a court may find that Congress impliedly preempted such claims by "conflict" if 1) compliance with both federal and state law is impossible, or 2) the claims would "stand[] as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." Crosby v. Nat'l Foreign Trade Council, 530 U.S. 363, 372-73

(2000) (quotation omitted). The district court concluded that each basis for conflict preemption was present. We disagree.

C.

The Supreme Court characterized "[i]mpossibility pre-emption [as] a demanding defense." Wyeth, 129 S.Ct. at 1199. To prevail on that defense, the generic defendants must show that compliance with both federal law and the state laws Mensing seeks to enforce is not merely difficult, but "a physical impossibility." Fid. Fed. Sav. & Loan Ass'n v. de la Cuesta, 458 U.S. 141, 153 (1982) (quotation omitted). The parties agree that generic labels must be substantively identical to the name brand label even after they enter the market. See, e.g., 21 C.F.R. § 314.150(b)(10) (FDA may withdraw approval of a generic drug if its label is "no longer consistent" with the name brand label); 57 Fed. Reg. at 17961, cmt. 39 (1992). Because of this requirement, the generic manufacturers argue they are prohibited from implementing a unilateral label change without prior FDA approval through the CBE process. Yet, 21 C.F.R. § 314.97 compels generic manufacturers to "comply with the requirements of §[] 314.70[.]" Section 314.70 includes the CBE process *and* the prior approval supplement process.[3] In this case we need not decide whether generic manufacturers may unilaterally

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[3] See supra sec. II-A for a discussion of these regulatory processes. If the defendants were correct that generic manufacturers can use the CBE process only to copy label changes initiated by the name brand manufacturer, it is curious that § 314.70(c) was never revised to distinguish between name brand and generic manufacturers.

enhance a label warning through the CBE procedure[4] because the generic defendants could have at least *proposed* a label change that the FDA could receive and impose uniformly on all metoclopramide manufacturers if approved.

The regulatory framework makes clear that a generic manufacturer must take steps to warn its customers when it learns it may be marketing an unsafe drug. Generic manufacturers are subject to the requirement that their labeling "shall be revised as soon as there is reasonable evidence of an association of a serious hazard with a drug[.]" 21 C.F.R. § 201.57(e). The generic defendants argue that they comply with this statute by simply ensuring that their labels match the name brand label. Mensing alleges that the Reglan manufacturers did nothing to strengthen the label despite reasonable evidence of the drug's association with a serious hazard. In these circumstances, § 201.57(e) does not permit generic manufacturers passively to accept the inadequacy of their drug's label as they market and profit from it.

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[4] The district court relied heavily on two FDA statements that no longer carry the same weight after Wyeth. In light of Wyeth, the FDA formally withdrew its amicus briefs in Colacicco v. Apotex, Inc., 432 F. Supp. 2d 514 (E.D.Pa. 2006); aff'd in part and rev'd in part, 521 F.3d 253 (3d Cir. 2008); vacated, 129 S. Ct. 1578 (2009). The other FDA statement appears in a footnote in the "Supplementary Information" section of a notice of proposed rule making for a regulation *not pertaining to generic drugs*. 73 Fed. Reg. 2848, 2849 n.1 (Jan. 16, 2008) ("CBE changes are not available for generic drugs."). Even the defendants admit that generic manufacturers can use the CBE process, § 314.97, to copy an updated name brand label. See also Demahy v. Wyeth, Inc., 586 F.Supp.2d 642, 655 (E.D.La. 2008), appeal docketed, No. 08-31204 (5th Cir. Dec. 16, 2008); Wyeth, 129 S.Ct. at 1201.

See Wyeth, 129 S.Ct. at 1202 ("The FDA has limited resources to monitor the 11,000 drugs on the market[.] . . . [M]anufacturers, not the FDA, bear primary responsibility for their drug labeling[.]"). The statute itself empowers the FDA to withdraw approval for a drug that is "misbranded" due to an insufficient label. 21 U.S.C. §§ 331(a)-(b), 352(a).

Interpretive commentary outside the regulations supports the requirement that at a minimum a generic manufacturer should alert the agency to any new safety hazard associated with its product. In commentary published contemporaneously to the adoption of the Hatch-Waxman Amendments, the FDA stated: "After approval of an ANDA, if an ANDA holder [a generic manufacturer] believes that new safety information should be added, *it should provide adequate supporting information to FDA*, and FDA will determine whether the labeling for the generic and listed drugs should be revised." 57 Fed. Reg. 17950, 17961 cmt. 40 (Apr. 28, 1992) (emphasis supplied).

Further, 21 C.F.R. § 314.98 requires that generic manufacturers follow the same record keeping and reporting of adverse drug experiences post marketing that name brand manufacturers must undertake. In discussing this provision, the FDA noted that "ANDA applicants [must] submit a periodic report of adverse drug experiences even if the ANDA applicant has not received any adverse drug experience reports *or initiated any labeling changes*." 57 Fed. Rep. 17950, 17965 cmt 53 (Apr. 28, 1992) (emphasis supplied). See also CDER, Guidance for Industry, Major, Minor, and Telephone Amendments to Abbreviated New Drug Applications 1-3 (Dec. 2001) (describing ANDA amendments addressing "labeling deficiencies" as

"minor amendments" that the FDA will attempt to review within 60 days).

Implicit in these comments is the FDA's expectation that generic manufacturers will initiate label changes other than those made to mirror changes to the name brand label and that the agency will attempt to approve such proposals quickly. The availability of one particular procedure (the CBE process, on which the district court expended the majority of its discussion) is immaterial to the preemption analysis in light of this clear directive to generic manufacturers and the availability of the prior approval process.

Because there is nothing in the FDCA or Hatch-Waxman Amendments that explicitly forbids them from proposing a label change through the prior approval process, the generic defendants cite regulatory language in § 314.70 to the effect that the prior approval procedure is for "major changes" while changes to enhance warnings are subject to the CBE procedure. Defendants' reading of § 314.70 is too restrictive. The section they cite establishes various methods of proposing changes to approved drugs. The more significant the change, the more notice the FDA needs prior to its implementation. The section repeatedly uses the nonrestrictive phrase "[t]hese changes include, but are not limited to" in order to describe the changes manufacturers can propose through each kind of supplement. §§ 314.70(b)(2), (c)(2), (d)(2). Section 314.70 does not evidence an FDA policy, let alone Congressional intent, to prevent generic manufacturers from proposing changes to a label's warning through the prior approval process. Indeed, manufacturers are *required* to use the prior approval process for "labeling changes" (with a few

exceptions including permissive use of the CBE process for warning enhancements, § 314.70(b)(2)(v)(A)).

In addition to proposing a label change, the generic manufacturers could have suggested that the FDA send out a warning letter to health care professionals. When the FDA first adopted its labeling regulations, well before the Hatch-Waxman Amendments, it stated that the requirements "do not prohibit a manufacturer . . . from warning health care professionals whenever possibly harmful adverse effects associated with the use of the drug are discovered." 44 Fed. Reg. 37434, 37447 (June 26, 1979); see also CDER, Manual of Policies and Procedures (MAPP) 6020.10, NDAs: "Dear Health Care Professional" Letters (July 2, 2003) (guidance document to name brand manufacturers stating that the letters may be ordered by the FDA or sent by manufacturers without FDA involvement).[5]

The generic defendants argue that they have no duty under the FDCA to propose stronger warnings, but the issue here is whether they have such a duty under state law. The question before this court is whether generic defendants can both fulfill a state law

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[5] Mensing argues that the generic defendants themselves could have warned their customers of the risk of tardive dyskinesia through such letters. The letters are considered regulated labeling, 21 C.F.R. §§ 202.1(l)(1), (2), and under the FDAAA, the FDA sends the letters out on behalf of ANDA holders if it determines that such a letter is a necessary part of a risk evaluation and mitigation strategy. 21 U.S.C. § 355-1(i)(2). Although the FDAAA was not in effect when Mensing took metoclopramide, it provides support for the defendants' contention that Congress did not intend that generic manufacturers send out "Dear Healthcare Provider" letters uncoordinated with other manufacturers of the drug.

duty to warn and comply with the FDCA. Does federal law forbid them from taking steps to warn their customers? The district court concluded that generic drug manufacturers "may seek to add safety information to a drug label" through the prior approval process or by requesting that the FDA send "Dear Health Care Professional" letters, but it remained uncertain what the FDA might have done had they proposed a label change. It therefore hesitated to impose liability based on speculation.

Subsequently, the Supreme Court made it clear in Wyeth that uncertainty about the FDA's response to such measures makes federal preemption less likely. "[A]bsent clear evidence that the FDA would not have approved a change to [the drug's] label, we will not conclude that it was impossible for [the manufacturer] to comply with both federal and state requirements." Wyeth, 129 S.Ct. at 1198; see also Grand River Enterprises Six Nations, Ltd. v. Beebe, 574 F.3d 929, 936 (8th Cir. 2009) ("[A] hypothetical or potential conflict is insufficient to warrant the pre-emption of the state statute."), citing Rice v. Norman Williams Co., 458 U.S. 654, 659 (1982).[6] To support preemption

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[6] The generic defendants argue that they would risk rescindment of their ANDA by implementing a unilateral label change through the CBE procedure without prior FDA approval. 21 C.F.R. § 314.150(b)(10). FDA commentary to § 314.150 makes clear that the section's purpose is to enforce the undisputed requirement that generic manufacturers change their label to match a name brand change. 57 Fed. Reg. 17950, 17970 cmt. 78 (Apr. 28, 1992). The issue of preemption does not rest on the availability of the CBE procedure, and hypothetical conflicts are not favored.

In Wyeth, the Supreme Court found it "difficult to accept" that "the FDA would bring an enforcement action against a manufacturer for strengthening a warning pursuant to the CBE

the generic defendants must show the likelihood of FDA *in*action. The record contains nothing, let alone "clear evidence," to suggest the FDA would have rejected a labeling proposal from any of them. In fact, earlier this year the FDA mandated that metoclopramide manufacturers enhance the label's warning of the risks of tardive dyskinesia. See Letter from Joyce Korvick, CDER (Feb. 26, 2009), available at http://www.fda.gov/downloads/Drugs/DrugSafety/.../UCM111376.pdf.

The generic defendants attempt to minimize the significance of Wyeth by focusing on Justice Breyer's one paragraph concurring opinion, in which he emphasized the majority's point that an agency could preempt state law through "lawful specific regulations[.]" Wyeth, 129 S.Ct. at 1204 (Breyer, J. concurring). The defendants cite no regulations specifically mandating preemption like those posed as examples in Wyeth, however. Id. at 1201, n.9. On the face of the regulations in effect, generic manufacturers must comply with the CBE procedure and maintain adequate warnings. 21 C.F.R. §§ 314.97, 201.57(e). As Judge William K. Sessions III has observed, Justice Breyer's concurrence "does not come close to a hint that an unofficial FDA interpretation at odds with the

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regulation." Wyeth, 129 S.Ct. at 1197. The defendants have not cited a single instance in which the FDA even threatened an enforcement action against a generic manufacturer for unilaterally enhancing its label warnings. Moreover, "[t]he FDCA does not provide that a drug is misbranded simply because the manufacturer has altered an FDA-approved label," the misbranding provisions focus on the accuracy of the label's substance, including the adequacy of its warnings. Id.; see also 21 U.S.C. §§ 355(e), id. at 352.

plain language of a regulation will have preemptive effect." Kellogg v. Wyeth, 612 F.Supp.2d 437, 442 (D.Vt. 2009) (concluding that Wyeth undermines preemption claims of generic manufacturers).

The generic defendants were not compelled to market metoclopramide. If they realized their label was insufficient but did not believe they could even propose a label change, they could have simply stopped selling the product. Instead, they are alleged to have placed a drug with inadequate labeling on the market and profited from its sales. If Mensing's injuries resulted from their failure to take steps to warn their customers sufficiently of the risks from taking their drugs, they may be held liable.

D.

Even if compliance with state and federal law is not impossible, state claims could still be preempted if they would obstruct the purposes and objectives of federal law. The generic defendants argue that proposing a label change would necessitate expensive clinical studies, thwarting the goal of the Hatch-Waxman Amendments to bring low cost generic drugs to market quickly. Yet the FDA did not conduct its own studies when it mandated an enhanced warning for metoclopramide. It simply referenced studies published elsewhere. Requests for label changes must be supported by scientific substantiation,[7] but there is

[7] Section 314.70(c)(6)(iii)(A) addresses CBE labeling changes to strengthen warnings; the applicable version during the period when Mensing took metoclopramide did not specify an evidentiary standard.

nothing to indicate that the information must be acquired through a manufacturer's own clinical tests. As a matter of fact, the Supreme Court concluded in Wyeth that multiple reports of an adverse experience with a drug provided the scientific substantiation to justify a manufacturer's request to change a label. Wyeth, 129 S.Ct. at 1197. Generic manufacturers are already required to collect and report adverse drug experiences with their products. 21 C.F.R. § 314.98, referencing 21 C.F.R. § 314. 80. Mensing alleges that if the generic manufacturers had merely taken note of the accumulation of adverse drug experiences reports and the published medical studies about metoclopramide, they would have had sufficient substantiation to warrant a label change.

The obligation Mensing seeks to impose upon generic manufacturers does not obstruct the purposes and objectives of the Hatch-Waxman Amendments in any way. On the contrary, "[f]ailure-to-warn actions," like Mensing's, "lend force to the FDCA's premise that manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times." Wyeth, 129 S.Ct. at 1202. The generic defendants argue that the Hatch-Waxman Amendments supply the relevant statutory framework, rather than the whole FDCA. Yet additions to the statute like the Hatch-Waxman Amendments must be considered part and parcel of the FDCA. These amendments provided for cheaper, expedited approval of generic drugs, not relief from the fundamental requirement of the FDCA that all marketed drugs remain safe. Congress and the FDA have long viewed state tort law as complementing, not obstructing, the goals of the FDCA. Wyeth, 129 S.Ct. at 1199-1200 (Congress "determined that widely available state rights of action

provided appropriate relief for injured [drug] consumers" and that "state-law remedies further consumer protection by motivating manufacturers . . . to give adequate warnings."); id. at 1197 ("[T]he statute contemplates that federal juries will resolve most misbranding claims[.]").

"If Congress had intended to deprive injured parties of a long available form of compensation, it surely would have expressed that intent more clearly." Bates v. Dow Agrosciences LLC, 544 U.S. 431, 449 (2005). Like the Fourth Circuit in Foster, 29 F.3d at170, we decline to assume that Congress intended to shield from tort liability the manufacturers of the majority of the prescription drugs consumed in this country and leave injured parties like Mensing no legal remedy.

III.

We turn next to Mensing's claims against the name brand manufacturers. Traditional products liability requires a plaintiff to show that she actually consumed the defendant's product. See, e.g., Bixler by Bixler v. Avondale Mills, 405 N.W.2d 428 (Minn. App. 1987). Although she never ingested name brand Reglan, Mensing claims that the name brand manufacturers are liable for various common law torts including negligent representation and fraud for misrepresenting the risks of tardive dyskinesia associated with metoclopramide.

Mensing's theory was rejected in Foster. There, the plaintiffs argued that "because generic drugs are required by federal law to be equivalent to their name brand counterparts," the name brand defendant should be responsible for representations or omissions on the

generic manufacturer's label. Foster, 29 F.3d at 169. The Fourth Circuit's response was that the plaintiffs were reframing products liability claims which they could not prove. Id. at 168. Presuming that generic manufacturers were responsible for altering their own labels when postapproval safety concerns arose, the court found no legal precedent to hold the name brand manufacturers liable for injuries caused by their competitors. Id. at 170 Subsequently, the overwhelming majority of courts considering this issue has reached the same conclusion.[8]

The Minnesota Court of Appeals is one of these courts. In Flynn v. American Home Products Corp., 627 N.W.2d 342 (Minn. App. 2001), a plaintiff like Mensing sought to hold name brand manufacturers liable for the harm caused by ingesting a generic equivalent. The court declined to recognize the "fraud on the FDA" claim essentially based on the name brand defendant's misrepresentations to the FDA about the drug's safety, and it also rejected an alternative argument based on Minnesota tort law. Id. at 350-52. Mensing argues that, unlike the Flynn plaintiffs, she did allege that the name brand defendants' representations "were relied upon by her physician when issuing the prescription." Id. at 349-50. Mensing cites only one court since Foster to have found such a factor determinative. Conte v. Wyeth, 85 Cal. Rptr. 3d 299 (Cal. Ct. App. 2008).

Whatever the merits of Conte under California law, the Flynn court concluded that "central" to a

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[8] Thirty two courts applying the laws of at least seventeen states, according to the defendants.

fraudulent misrepresentation claim under Minnesota law is "a suppression of facts which one party is under a legal or equitable obligation to communicate to the other, and which the other party is entitled to have communicated to him." Flynn, 627 N.W.2d at 350 (quotations omitted). In other words, regardless of whether her doctor relied upon the Reglan label, Mensing must show that the name brand manufacturers owed *her* a duty of care. Duty is a threshold requirement for all of the tort claims Mensing asserts.[9] See, e.g., Noble Systems Corp. v. Alorica Central, LLC, 543 F.3d 978, 985 (8th Cir. 2008) (finding that under Minnesota law negligent misrepresentation requires the plaintiff to "prove some relationship that is sufficient to create a duty owed by the defendant to the plaintiff").

Such a duty of care does not extend to all potential Reglan consumers. "Minnesota common law . . . requires a stronger relationship and a direct communication." Flynn, 627 N.W.2d at 350. Since Mensing "did not purchase or use [the name brand defendants'] product, . . . there was no direct relationship between them, let alone a fiduciary

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[9] Mensing's attempt to characterize her fraud claim as a type requiring no proof of a duty of care is unavailing. A plaintiff claiming fraud in Minnesota must show that the defendant intended to induce another to act in reliance on its fraudulent statement. Specialized Tours, Inc. v. Hagen, 392 N.W.2d 520, 532 (Minn. 1986). Mensing's relationship with the Reglan manufacturers is too attenuated, and she has cited no Minnesota case in which the court imposed liability for fraud on a defendant who did not intend to communicate with the plaintiff. The Reglan manufacturers intended to communicate with their customers, not the customers of their competitors.

relationship that gave rise to a duty." Id. at 350. Mensing focuses on the foreseeability of harm from the defendants' action. Like the Fourth Circuit, we conclude that holding name brand manufacturers liable for harm caused by generic manufacturers "stretch[es] the concept of foreseeability too far." Foster, 29 F.3d at 171. As for Mensing's negligent misrepresentation claim, "the Minnesota Supreme Court has recognized negligent misrepresentation involving damages only for pecuniary loss[.]" Flynn, 627 N.W.2d at 350, citing Smith v. Brutger Cos., 569 N.W.2d 408, 414 (Minn. 1997). We find it unlikely the Minnesota Supreme Court would extend the doctrine to misrepresentation involving the risk of physical harm in these circumstances. We conclude that under Minnesota law Mensing has not shown that the name brand manufacturers owed her a duty of care necessary to trigger liability.

IV.

In sum, we conclude that Mensing has stated a viable claim against the generic metoclopramide manufacturers. Far from prohibiting them from taking steps to warn their customers of new safety hazards, federal law requires such action. For the reasons stated we reverse the judgment in favor of the generic manufacturers but affirm the judgment as to the name brand manufacturers.

RELEVANT DOCKET ENTRIES

U. S. District Court
Eastern District of Louisiana (New Orleans)
CIVIL DOCKET FOR CASE #:
2:08-cv-03616-CJB-JCW

Demahy v. Wyeth Inc., et al.

Date Entered	#	Docket Text
06/03/2008	1	NOTICE OF REMOVAL from 22nd Judicial District Court for the Parish of St. Tammany, case number 2008-12332 "A". (Filing fee $ 350)filed by Wyeth, Inc.. (Attachments: # 1 Civil Cover Sheet, # 2 Exhibit A (State Court Complaint), # 3 Exhibit B, # 4 Exhibit C, # 5 Exhibit D)(sdd,) Modified on 6/4/2008 (sdd,). (Entered: 06/03/2008)
06/06/2008	3	ANSWER to Complaint with Jury Demand by Actavis Inc..(Ryan, Elizabeth) (Entered: 06/06/2008)
07/29/2008	19	MOTION to Dismiss Party by Actavis Inc.. Motion Hearing set for 8/20/2008 09:30 AM before Judge Carl Barbier. (Attachments: # 1 Memorandum in Support, # 2 Notice of Hearing, # 3 Proposed Order, # 4 Exhibit, # 5 Exhibit, # 6 Exhibit, # 7 Exhibit, # 8 Exhibit, #

Date Entered	#	Docket Text
		9 Exhibit)(Ryan, Elizabeth) (Entered: 07/29/2008)
09/09/2008	29	RESPONSE/MEMORANDUM in Opposition filed by Julie Demahy re 19 MOTION to Dismiss Party. (Attachments: # 1 Exhibit A, # 2 Exhibit B-1, # 3 Exhibit B-2, # 4 Exhibit C-1, # 5 Exhibit C-2)(Tonry, Richard) (Entered: 09/09/2008)
09/16/2008	34	REPLY to Response to Motion filed by Actavis Inc. re 19 MOTION to Dismiss Party. (Attachments: # 1 Exhibit A, # 2 Exhibit B, # 3 Exhibit C)(sek,) (Entered: 09/16/2008)
10/28/2008	36	ORDER & REASONS: granting in part and denying in part 19 Motion to Dismiss. ORDERED that Actavis's Rule 12(b)(6) Motion to Dismiss Demahy's LPLA failure-to-warn claims under a theory of federal conflict preemption is hereby DENIED. FURTHER ORDERED that Actavis's Rule 12(b)(6) Motion to Dismiss Demahy's claims, to the extent that they allege fraud-on-the-FDA claims under Louisiana law, is hereby GRANTED. Signed by Judge Carl Barbier on 10/27/2008. (mmm,) (Entered: 10/28/2008)

Date Entered	#	Docket Text
11/13/2008	39	EXPARTE/CONSENT MOTION to Amend/Correct 36 Order on Motion to Dismiss Party, by Actavis Inc.. (Attachments: # 1 Memorandum in Support to Include Statement Certifying An Interlocutory Appeal (28 U.S.C. 1292(b)), # 2 Proposed Order)(Ryan, Elizabeth) (Entered: 11/13/2008)
11/17/2008	40	ORDER granting 39 MOTION to Amend/Correct re: 36 Order on Motion to Dismiss Party/MOTION to Amend/Correct: The Court finds and certified that this Order involves a controlling question of law as to which there is substantial ground for difference of opinion and that an immediate appeal from the Order may materially advance the ultimate termination of the litigation. Signed by Judge Carl Barbier on 11/14/2008.(mmm,) (Entered: 11/17/2008)
11/20/2008	41	ORDER: This action is closed for statistical purposes. FURTHER ORDERED that the Court shall retain jurisdiction and that the case shall be restored to the trial docket upon motion of a party if circumstances change, so that it may proceed to final disposition; this order shall not prejudice the

Date Entered	#	Docket Text
		rights of the parties to this litigation. Accordingly, all deadlines in this litigation are hereby STAYED pending the filing and disposition of the interlocutory appeal. Signed by Judge Carl Barbier on 11/20/2008.(mmm,) (Entered: 11/20/2008)
12/18/2008	42	NOTICE OF INTERLOCUTORY APPEAL by Actavis Inc. as to 40 Order. Appeal #08-31204. (Attachments: # 1 Letter from USCA)(sek,) (Entered: 12/18/2008)
02/05/2010	48	USCA JUDGMENT issued as mandate on 2/1/2010 as to 42 Notice of Interlocutory Appeal filed by Actavis Inc. ORDERED: The Judgment of the District Court is affirmed. USCA judge name: KING, HIGGINBOTHAM, CLEMENT. (Attachments: # 1 Opinion)(mmm,) (Entered: 02/05/2010)

General Docket
United States Court of Appeals
for the 5th Circuit

No. 08-31204

Demahy v. Wyeth Inc.

12/16/2008	Private civil diversity case docketed. NOA filed by Appellant Actavis Inc. [08-31204] (PAC)
02/10/2009	Appellant's Brief filed by Appellant Actavis Inc. Disk Provided [Y/N]: Y Sufficient [Y/N]: Y [6215561-1] [08-31204] A/Pet's Brief ddl satisfied. E/Res's Brief due on 3/12/09 for Julie Demahy. (NFD)
02/10/2009	Addendum to brief filed by Appellant Actavis Inc. No. of pages: Volumes 1 & 2. [08-31204] (NFD)
02/10/2009	Record excerpts filed by Appellant Actavis Inc. Disk Provided [Y/N]: Y Sufficient [Y/N]: N - over 40 pages of optional contents [08-31204] Sufficient Record Excerpts due on 2/20/09 for Actavis Inc. (NFD)
02/12/2009	RECORD EXCERPTS MADE SUFFICIENT filed by Appellant Actavis Inc in 08-31204 [6215646-2]. [08-31204] (NFD)
02/17/2009	AMICUS CURIAE BRIEF FILED by Amicus PLIVA INC. The Consent is

	Included in the Brief. # of Copies Provided: 7 [08-31204] (NFD)
03/30/2009	APPELLEE'S BRIEF FILED by Ms. Julie Demahy.. # of Copies Provided: 7 E/Res's Brief deadline satisfied. Reply Brief due on 04/13/2009 for Appellant Actavis Inc [08-31204] (NFD)
04/14/2009	APPELLANT'S REPLY BRIEF FILED by Actavis Inc.. # of Copies Provided: 8 Reply Brief deadline satisfied [08-31204] (NFD)
07/21/2009	SUPPLEMENTAL AUTHORITIES (FRAP 28j) FILED by Appellee Ms. Julie Demahy [08-31204] (PFT)
07/29/2009	SUPPLEMENTAL AUTHORITIES (FRAP 28j) FILED by Appellant Actavis Inc [08-31204] (PFT)
08/05/2009	ORAL ARGUMENT HEARD before Judges King, Higginbotham, Clement. Arguing Person Information Updated for: Louis M. Bograd arguing for Appellee Julie Demahy; Arguing Person Information Updated for: Richard A Dean arguing for Appellant Actavis Inc [08-31204] (PFT)
08/05/2009	ORAL ARGUMENT panel has requested of the parties the following: Suppplemental Letter Brief. A/Pet Supplemental Brief Due on 08/10/2009 for Appellant Actavis Inc.. E/Res Supplemental Brief due on 08/10/2009 for Appellee Julie Demahy. [08-31204] (PFT)

08/10/2009	APPELLANT'S SUPPLEMENTAL BRIEF FILED by Actavis Inc. # of Copies Provided: 4 [08-31204] (MLF)
08/10/2009	APPELLEE'S SUPPLEMENTAL BRIEF FILED by Ms. Julie Demahy. # of Copies Provided: 4 E/Res's Supplemental Brief deadline satisfied [08-31204] (MLF)
10/09/2009	SUPPLEMENTAL AUTHORITIES (FRAP 28j) FILED by Appellee Ms. Julie Demahy [08-31204] (NFD)
10/16/2009	RESPONSE/OPPOSITION filed by Actavis Inc [6388521-1] to the 28j letter filed by Appellee Ms. Julie Demahy in 08-31204. [6384350-2] Date of Service: 10/15/2009 [08-31204] (MLF)
11/09/2009	SUPPLEMENTAL AUTHORITIES (FRAP 28j) FILED by Appellee Ms. Julie Demahy [08-31204] (NFD)
12/04/2009	SUPPLEMENTAL AUTHORITIES (FRAP 28j) FILED by Appellee Ms. Julie Demahy Date of Service: 12/03/2009 [08-31204] (NFD)
12/07/2009	SUPPLEMENTAL AUTHORITIES (FRAP 28j) FILED by Appellant Actavis Inc Date of Service: 12/04/2009 [08-31204] (MLF)
01/08/2010	PUBLISHED OPINION FILED. [08-31204 Affirmed] Judge: CDK , Judge: PEH , Judge: EBC. Mandate pull date is 01/29/2010 [08-31204] (ARC)
01/08/2010	JUDGMENT ENTERED AND FILED. [08-31204] (ARC)

02/01/2010 MANDATE ISSUED. Mandate pull date satisfied. [08-31204] (NFD)

22ND JUDICIAL DISTRICT COURT
FOR THE PARISH OF ST. TAMMANY

STATE OF LOUISIANA

NO. 2008-12332 DIVISION "A"

[Filed April 28, 2008]

JULIE DEMAHY	)
	)
VERSUS	)
	)
WYETH, INC. d/b/a WYETH, Individually and as Successor-in-Interest of A.H. ROBINS COMPANY, INC., SCHWARZ PHARMA, INC., and ACTAVIS INC., Individually and as Successor-in-Interest of PUREPAC PHARMACEUTICAL CO.	)

Filed: APR 28 2008 S/EVELYN J. WELSH
DEPUTY CLERK

PETITION FOR DAMAGES

NOW INTO COURT, through undersigned counsel, comes petitioner, **JULIE DEMAHY**, a person of the full age of majority and a resident of and domiciled in St. Tammany Parish, Louisiana, who respectfully submits the following petition for damages:

1.

Made defendants herein are:

A. **WYETH, INC. d/b/a WYETH ["WYETH"], Individually and as Successor-in-Interest of A.H. ROBINS COMPANY, INC. WYETH** is a Delaware corporation with its principal place of business at 5 Giralda Farms, Madison, New Jersey 07940, and is the successor-in-interest to A.H. Robins Company, Inc., a Virginia corporation that first obtained approval by the Food and Drug Administration to distribute metoclopramide, under the brand name of Reglan, in the United States. Upon information and belief, until December 27, 2001, **WYETH** manufactured and distributed Reglan through its Wyeth-Ayerst Laboratories Division in St. Davids, Pennsylvania. Metoclopramide is the active ingredient of Reglan. Upon information and belief, on December 27, 2001, **WYETH** sold the rights and liabilities associated with Reglan tablets to Schwarz Pharma, Inc. At all material times, **WYETH** was engaged in the business of testing, developing, manufacturing, labeling, marketing, distributing, promoting and/or selling, either directly or indirectly, through third parties, as successor in interest, or related entities, metoclopramide tablets in the State of Louisiana and in interstate commerce.

The registered agent for service for **WYETH** is The Prentice Hall Corp. System, 40 Technology Parkway South, #300, Norcross, Kentucky 30092.

B. **SCHWARZ PHARMA, INC.** ["**SCHWARZ**"], a Delaware corporation. Upon information and belief, on December 27, 2001, **SCHWARZ** purchased the rights and liabilities associated with metoclopramide tablets from **WYETH** pursuant to an Asset Purchase Agreement wherein **SCHWARZ** obligated itself to the responsibility of claims relating to or arising out of the ingestion or use of metoclopramide from and after

March 31, 2002, subject to a right of indemnification by **WYETH**. At all material times, **SCHWARZ** was engaged in the business of testing, developing, manufacturing, labeling, marketing, distributing, promoting and/or selling, either directly or indirectly, through third parties, as successor in interest, or related entities, metoclopramide tablets, known by brand name as Reglan, in the State of Louisiana and in interstate commerce.

The registered agent for service for **SCHWARZ** is CSC Entity Services, LLC, 2711 Centerville Road, Suite 400, Wilmington, DE 19808.

C. **ACTAVIS INC., Individually and as Successor-in-Interest of PUREPAC PHARMACEUTICAL CO.** ["**ACTAVIS**"], a Delaware corporation which merged with Purepac Pharmaceutical Co. and as such obligated itself to the responsibility of claims relating to or arising out of the ingestion or use of metoclopramide. At all material times, **ACTAVIS** was engaged in the business of testing, developing, manufacturing, labeling, marketing, distributing, promoting and/or selling, either directly or indirectly, through third parties, as successor in interest, or related entities, metoclopramide tablets, known by brand name as Reglan, in the State of Louisiana and in interstate commerce.

The registered agent for service for **ACTAVIS** is United Corporate Services, INC., 874 Walker Road, Suite C, Dover, DE 19904.

All defendants, identified *supra,* inclusive, and each of them, may be referred to in this complaint

collectively as the "Defendants" and are liable to plaintiff, individually, jointly, severally, and in solido.

2.

At all relevant times, the Defendants were acting by and through their agents, servants and/or employees, each of whom were acting within the scope and course of their employment by agency or authority on their behalf.

3.

At all relevant times, the Defendants were in the business of researching, designing, formulating, compounding, testing, manufacturing, producing, processing, assembling, inspecting, distributing, marketing, labeling, promoting, packaging and/or advertising the pharmaceutical drugs known and/or branded Reglan and/or the generic equivalent, metoclopramide HCl and/or metoclopramide in the State of Louisiana and in interstate commerce.

4.

At all relevant times, defendants did manufacture, create, design, assemble, test, label, sterilize, package, distribute, promote, supply, market, sell, advertise, and/or otherwise distribute in the State of Louisiana and in interstate commerce Reglan and/or metoclopramide tablets.

5.

At all relevant times, defendants sold, delivered and/or distributed such products for ultimate sale

and/or use by consumers, including plaintiff, within the State of Louisiana and in interstate commerce.

6.

This Honorable Court has jurisdiction over this case because the defendants conducted business in the State of Louisiana through pharmaceutical sales representatives and were engaged in testing, developing, manufacturing, labeling, marketing, distributing, promoting and/or selling, either directly or indirectly, through third parties or related entities Reglan and/or metoclopramide tablets; thus, there exists a sufficient nexus between the defendants forum contacts and the plaintiff's claims to justify assertion of jurisdiction in the State of Louisiana.

7.

Venue of this action is proper in this Court as the acts of negligence occurred within the Parish of St. Tammany, State of Louisiana.

8.

In October 2002, plaintiff's physician prescribed Reglan for the treatment of gastroesophageal reflux disease (GERD).

9.

Plaintiff's pharmacy, Walgreens, filled plaintiff's prescriptions for Reglan with the generic equivalent, metoclopramide.

10.

Plaintiff ingested the prescription drug Reglan and/or metoclopramide as prescribed until the end of April 2007.

11.

The terms Reglan and metoclopramide are commonly employed to refer to all metoclopramide products, including the brand name product and its generic equivalents.

12.

Metoclopramide is a prokinetic drug that helps control GERD by blocking dopamine receptors in the brain and throughout the body which enhances movement or contractions of the esophagus, stomach and intestines.

13.

On or about October 19, 2007, plaintiff was evaluated at the University of Texas, Southwestern Medical Center in Dallas, Texas, wherein she was diagnosed as having tardive dyskinesias caused by long-term use of Reglan and/or metoclopramide. That is, plaintiff's long term ingestion of Reglan and/or metoclopramide resulted in overexposure to the drug which caused her to suffer serious, permanent and disabling neurological injuries, including but not limited to, injuries of or associated with the central nervous and extrapyramidal motor systems, specifically Tardive Dyskinesia.

14.

Because of the injuries plaintiff suffered as a result of her use of Reglan and/or metoclopramide, plaintiff has experienced and will continue to experience medical and related expenses, loss of income, loss of ability to perform household services, disfigurement, disability, pain and suffering, psychological injury and other injuries and damages.

15.

Plaintiff's serious and permanent injuries came about as a foreseeable and proximate result of the Defendants dissemination of inaccurate, misleading, materially incomplete, false and otherwise inadequate information concerning the potential effects of exposure to and ingestion of Reglan and/or metoclopramide to the medical community, physicians, plaintiff's physicians, plaintiff and other foreseeable users of the drug.

16.

Reglan and/or metoclopramide is and was not approved by the United States Food and Drug Administration ["FDA"] for long-term use.

17.

Because of the misleading information that the Defendants provided to physicians and the FDA about the true risks associated with the use of Reglan and/or metoclopramide and because of their failure to adequately inform physicians generally, including plaintiff's physician, about the true risks associated

with the use of Reglan and/or metoclopramide, at all relevant times while plaintiff was taking Reglan and/or metoclopramide, her physicians never informed her of any side effects associated with Reglan and/or metoclopramide or that it was only approved by the FDA for short term use of up to 12 weeks.

18.

At all materials times, the Defendants were aware of the serious side effects caused by Reglan and/or metoclopramide including, but not limited to, central system disorders, depression with suicidal ideation, akathisia, tardive dyskinesia, tardive dystonia, visual disturbances and interference with drug metabolism.

19.

Pursuant to FDA regulations, the Defendants knew that they must fully, truthfully and accurately disclose to the FDA data and information regarding the drug's chemistry, proposed manufacturing process, proposed model labeling which includes warnings about risks and side effects, test results for the drug, results of animal studies, results of clinical studies and the drug's bioavailability, because the data and information would be relied upon by the medical community, physicians, plaintiff's physician, plaintiff and other like foreseeable users of Reglan and/or metoclopramide once approved.

20.

The defendants failed to fully, truthfully and accurately disclose Reglan and/or metoclopramide data to the FDA and as a result, intentionally and

fraudulently misled the medical community, physicians, plaintiff's physician and plaintiff about the risks associated with long term use of metoclopramide.

21.

Under FDA regulations, the Defendants have a duty to ensure its warnings to the medical community are accurate and adequate; a duty to conduct safety surveillance of adverse events for the drug; and to report any data related to the safety and/or accuracy of the warnings and information disseminated regarding the drug.

22.

The defendants knowingly, intentionally and negligently disseminated misleading information to physicians across the country through the *Physician's Desk Reference*, labeling information for Reglan and/or metoclopramide, which misled the medical community, physicians and plaintiff's physician about the increased risk of extrapyramidal side effects, including tardive dyskinesia.

23.

At all material times, the Defendants knew or should have known that most physicians were not aware of or did not fully appreciate the seriousness of the risks associated with use of Reglan and/or metoclopramide and that, consequently, there was a widespread tendency for physicians to prescribe these drugs for inappropriate long-term use.

24.

The Defendants knew or should have known that the package insert and the Physician's Desk Reference monograph for Reglan did not adequately inform physicians about the risks associated with Reglan and/or metoclopramide.

25.

The Defendants had access to and knew that severe side effects would result from the use of Reglan and/or metoclopramide in the manner in which physicians were prescribing Reglan and/or metoclopramide and the fact that physicians did not fully understand the risks associated with Reglan and/or metoclopramide through the Defendants participation, individually and jointly, in or its ability to review data from clinical studies that were not publicly available, through its review of domestic and international medical literature concerning Reglan and/or metoclopramide, and/or through ongoing litigation.

26.

The Defendants failed to adequately warn physicians about the risks associated with Reglan and/or metoclopramide despite the fact that they knew physicians, the medical community, the generic pharmaceutical industry, plaintiff and others similarly situated relied on defendants to disclose what they knew or should have known from a prudent review of the information they possessed or to which they had access.

27.

Upon information and belief, defendant **WYETH** as Successor-in-Interest of A.H. ROBINS COMPANY, INC. expressly warranted to some physicians that Reglan and/or metoclopramide was safe in long-term use, knowing that physicians would share the information with other physicians in their community and that the physicians would come to rely on the express warranties which were false.

28.

The Defendants knew or should have known, through the exercise of reasonable care, that the package insert for Reglan and/or metoclopramide contained false and/or misleading statements and omitted information material to the foreseeable and ordinary contemplated uses of the drugs and, specifically grossly understating the prevalence of acute and long term side effects of Reglan and/or metoclopramide.

29.

The Defendants failed to use reasonable care to modify the package insert to adequately warn physicians about the true risks of both short and long term use, even after several injured patients filed lawsuits alleging inadequate warnings and produced competent expert testimony supporting their allegations.

30.

The Defendants had actual knowledge, through their own studies and studies by independent investigators, that physicians frequently prescribed Reglan and/or metoclopramide for long term use (more than 12 weeks) that was not safe for patients.

31.

The Defendants were further armed with knowledge that research by independent investigators revealed that the risk of tardive dyskensia and other extrapyramidal side effects of Reglan and/or metoclopramide in patients who received the drug for long term use was as much as 100 times greater than the 1 in 500 as disclosed in the package insert and/or the *Physician's Desk Reference*.

32.

The defendants ignored the numerous published medical literature pertaining to independent studies concerning the frequency of tardive dyskinesia.

33.

The Defendants had a duty and obligation to disclose to plaintiff and her physicians the true facts concerning Reglan and/or metoclopramide in that it was dangerous and defective and the actual likelihood that it was to cause serious consequences to users, including tardive dyskinesia, and the true level of risk involved in prescribing such drugs for the purposes indicated.

34.

At all material times, the Defendants intentionally, willfully and maliciously concealed or suppressed the true facts concerning Reglan and/or metoclopramide in that long term use and exposure could cause central nervous system side effects, depression with suicidal ideation, akathisia, tardive dyskinesia and tardive dystonia.

35.

At all material times, neither plaintiff nor her physicians were aware of the facts set forth herein and had they been, they would not have acted as they did by utilizing Reglan and/or metoclopramide to treat plaintiff's GERD.

36.

As a proximate result of the concealment or suppression of the facts set forth above, plaintiff was prescribed and ingested Reglan and/or metoclopramide and subsequently became ill sustaining the injuries and damages set forth above.

37.

The Defendants are liable as the manufacturers, distributors and/or sellers of the drugs Reglan and/or metoclopramide in violation of the Louisiana Products Liability Act, *La. R.S. 9:2800.51, et seq.*

38.

Reglan and/or metoclopramide was defective in design and/or formulation in that, when it left the control of Defendants and/or their representatives, the foreseeable risks of serious harm posed by the drug outweighed its alleged benefits. The foreseeable risks of serious harm were so great that plaintiff, having known of such foreseeable risks and alleged benefits, would not have ingested Reglan and/or metoclopramide.

39.

Reglan and/or metoclopramide was placed into the stream of commerce by Defendants acting through authorized agents, servants, employees and/or representatives. Plaintiff was prescribed Reglan and/or metoclopramide by her physicians and used the drug in a manner foreseeable by Defendants.

40.

The Reglan and/or metoclopramide ingested by plaintiff was expected to and did reach plaintiff without substantial change in its condition as tested, manufactured, designed, labeled, packaged, marketed and distributed. As a result of the use of Reglan and/or metoclopramide, plaintiff suffered serious, permanent and disabling neurological injuries, including but not limited to, injuries of or associated with the central nervous and extrapyramidal motor systems, specifically Tardive Dyskinesia.

41.

Reglan and/or metoclopramide was marketed to physicians to be prescribed to their patients and was marketed and advertised directly to the consuming public. Reglan and/or metoclopramide, as manufactured and supplied to healthcare professionals and the general public, was unaccompanied by proper warnings regarding the serious risks of ingesting the drug. Further, Defendants failed to warn of these serious risks after Defendants had knowledge of same. The information provided to consumers did not reflect Defendants' knowledge that Reglan and/or metoclopramide was not safe and effective as indicated in its aggressive marketing campaign nor were consumers such as plaintiff made aware that ingesting the drug could result in serious, permanent and disabling neurological injuries, including but not limited to, injuries of or associated with the central nervous and extrapyramidal motor systems, specifically Tardive Dyskinesia. Full and proper warnings that accurately and fully reflected the unreasonable risk of central nervous system side effects, depression, akathisia, akinesia, tardive dyskinesia, tardive dystonia, visual disturbances and/or interference with drug metabolism due to the ingestion of Reglan and/or metoclopramide should have been disclosed by Defendants.

42.

Plaintiff was prescribed Reglan and/or metoclopramide by her physician and used the drug in a manner reasonably foreseeable by Defendants. Reglan and/or metoclopramide was expected to and did reach plaintiff without substantial change in its

condition as tested, manufactured, designed, labeled, packaged, marketed and distributed. Plaintiff was not aware of and could not have reasonably discovered the unreasonably dangerous nature of Reglan and/or metoclopramide. As the producing cause and the legal and direct result of the failure to warn consumers of the defective condition of Reglan and/or metoclopramide, as manufactured and supplied by Defendants and their representatives, plaintiff ingested Reglan and/or metoclopramide and subsequently became ill, thereby sustaining the injuries and damages set forth herein.

43.

Defendants, through their agents, servants, employees and/or representatives, employed deception, fraud, false pretense, false promise, misrepresentation, unfair practice and the concealment, suppression, and omission of material facts in connection with the sale or advertisement of Reglan and/or metoclopramide, in violation of the Louisiana *Unfair Trade Practices and Consumer Protection Law, La. R.S. 51:1401, et seq.*

44.

Defendants' offer for sale of a consumer product, namely Reglan and/or metoclopramide, in trade or commerce, constitutes a representation that the product is reasonably safe for its intended purpose and intended use.

45.

Defendants have engaged in deceptive acts or practices, in violation of the Louisiana *Unfair Trade*

Practices and Consumer Protection Law, by knowingly, intentionally and/or recklessly omitting, concealing, and/or suppressing its own data from investigations and clinical trials, other analyses, studies, tests, understandings, and conclusions about the true efficacy and safety of Reglan and/or metoclopramide.

46.

Defendants violated the Louisiana *Unfair Trade Practices and Consumer Protection Law* by intentionally omitting, concealing and/or suppressing, or otherwise failing to communicate and notify the medical community, the plaintiff, and other consumers of Reglan and/or metoclopramide, of the negative safety information they possessed.

47.

Defendants deceptive acts were intended to induce the plaintiff to buy Reglan and/or metoclopramide.

48.

Because of the concealment, plaintiff was actually deceived and caused to suffer serious and permanent injuries and actual damages as set forth above.

49.

Defendants made material representations that were false and that were either known to be false when made or were asserted without knowledge of their truth. Defendants possessed adverse drug event reports, drug studies, and other documentation about Reglan and/or metoclopramide yet made numerous

misrepresentations regarding the frequency of related adverse occurrences in their package insert or *Physicians Desk Reference* label; as to the existence, occurrences and frequency of occurrences as well as the severity and extent of the overall risk of the drugs use; as to the efficacy of the drugs; as to the number of adverse events with use; and the seriousness and severity of adverse events reported with the use of the drugs.

50.

The misrepresentations by Defendants was the proximate cause and cause-in-fact of plaintiff's injuries.

51.

Defendants owed plaintiff legal duties in connection with their development, manufacturing, and distribution of Reglan and/or metoclopramide. Defendants breached those duties which was the proximate cause and cause in fact of plaintiff's injuries. Specifically, defendants failed to meet their duty to use reasonable care in the testing, creating, designing, manufacturing, labeling, packaging, marketing, selling and warning of Reglan and/or metoclopramide. Defendants are liable for the acts and/or omissions amounting to negligence and/or gross negligence.

WHEREFORE, plaintiff prays that defendants be served with a copy of this petition and duly cited to appear and answer same and after due proceedings, there be judgment rendered in favor of plaintiff, **JULIE DEMAHY**, and against **WYETH, INC. d/b/a WYETH, Individually and as Successor-in-**

Interest of A.H. ROBINS COMPANY, INC., SCHWARZ PHARMA, INC. AND ACTAVIS INC., Individually and as Successor-in-Interest of PUREPAC PHARMACEUTICAL CO. for all damages listed and considered reasonable in the premises, together with all costs of these proceedings, attorney fees and penalties, and legal interest from the date of judicial demand until paid, and all other general and equitable relief.

Respectfully Submitted,

TONRY, BRINSON & GLORIOSO, LLC

/s/ Richard A. Tonry, II
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JULE DEMAHY

[*Service List omitted in printing of this appendix*]

* * *

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA

CIVIL ACTION
NO. 08-3616

SECTION SECT. J MAG. 2

[Filed June 2, 2008]

JULIE DEMAHY	)
	)
VERSUS	)
	)
WYETH, INC. D/B/A WYETH, INDIVIDUALLY AND AS SUCCESSSOR IN INTEREST OF A.H. ROBINS COMPANY, INC., SCHWARZ PHARMA, INC., AND ACTAVIS INC., INDIVIDUALLY AND AS SUCCESSOR IN INTEREST OF PUREPAC PHARMACEUTICAL CO.	)

NOTICE OF REMOVAL

JURY TRIAL REQUESTED

TO: THE HONORABLE JUDGES OF THE UNITED STATES DISTRICT COURT FOR THE EASTERN DISTRICT OF LOUISIANA

United States Courthouse
New Orleans, Louisiana

Now comes Petitioner, Wyeth, through undersigned counsel, pursuant to 28 U.S.C. §§1441(a) and 1446, and files its Notice of Removal of this case from the 22nd Judicial District Court for the Parish of St. Tammany to the United States District Court for the Eastern District of Louisiana. Wyeth files this Notice of Removal with full reservation of any and all rights, defenses and objections, including but not limited to, insufficiency of process, insufficiency of service of process, lack of personal jurisdiction, improper venue, lack of procedural capacity, improper cumulation, no right of action, lack of standing, prescription, preemption, and no cause of action. The grounds for removal are as follows:

Plaintiff's State Court Allegations

1.

A "Petition for Damages" was filed on April 28, 2008 against Wyeth, Inc. ("Wyeth"), Schwarz Pharma, Inc. ("Schwarz"), and Actavis Inc. ("Actavis") in the 22nd Judicial District Court for the Parish of St. Tammany, State of Louisiana, entitled, "Julie DeMahy v. Wyeth, Inc. d/b/a/ Wyeth, individually and as successor in interest of A.H. Robins Company, Inc., Schwarz Pharma, Inc. and Actavis Inc., individually and as successor in interest of Purepac Pharmaceutical Co.," docket no. 2008-12332. A copy of the Petition is attached as Exhibit "A." To the best knowledge of the undersigned counsel, this is the only document appearing in the state court record in this matter as of the date of filing of this Notice. No defendant has heretofore filed an answer to the state court action.

2.

The Petition names Wyeth, Inc. d/b/a/ Wyeth, individually and as successor in interest of A.H. Robins Company, Inc., Schwarz and Actavis, individually and as successor in interest of Purepac Pharmaceutical, as defendants. *See* Petition, p. 1.

3.

The Petition was served on May 15, 2008 upon Wyeth and Purepac/Actavis, and May 16, 2008 on Schwarz. The Petition was the first pleading received by any defendant setting forth the claim for relief upon which this action is based. A copy of the Citation is attached as Exhibit "B."

4.

On information and belief, as of the date of the filing of this removal, there have been no proceedings other than the filing and service of the Petition in the 22nd Judicial District Court, Parish of St. Tammany, State of Louisiana.

5.

Pursuant to 28 U.S.C. § 1446 (b), this Notice of Removal is timely filed within thirty (30) days of first receipt by any defendant of plaintiff's original state court pleading.

Removal on Diversity Grounds

6.

This civil action is a matter over which this Court has original jurisdiction by virtue of 28 U.S.C. § 1332, and is one that may be removed to this Court by Wyeth under the provisions of 28 U.S.C. § 1441(b) in that it is a civil action in which all properly joined defendants are diverse from plaintiff, plaintiff's claims involve an amount in controversy exceeding $75,000, exclusive of interest and costs, and all properly joined defendants have consented to removal.

7.

On information and belief, at the time plaintiff commenced this action in Louisiana state court and at the time of the filing of this Notice of Removal, plaintiff was and is a citizen of the State of Louisiana.

8.

At the time of filing plaintiff's Complaint, defendant Wyeth was and is now a Delaware corporation with its principal place of business in the State of New Jersey. Schwarz is a Delaware corporation with its principal place of business in Georgia. Actavis is a Delaware corporation with its principal place of business in New Jersey. Purepac Pharmaceutical Co. is no longer in existence. Purepac was not headquartered in Louisiana nor did it have a principal place of business in Louisiana.

9.

Based on the foregoing and the allegations in the petition, there is complete diversity of citizenship between plaintiff and defendants.

The Amount in Controversy

10.

Although plaintiff pleads no specific amount of damages, in conformity with Louisiana Code of Civil Procedure article 893, the amount in controversy in this alleged products liability action clearly exceeds the sum or value of $75,000, exclusive of interest and costs. Evidence which supports that the required amount in controversy exceeds $75,000 is provided by plaintiff's Petition, which alleges that she developed tardive dyskinesia "which caused her to suffer serious, permanent and disabling neurological injuries." *See* Petition at ¶13. Plaintiff seeks damages for "medical and related expenses", "loss of income", "pain and suffering", "disability", "psychological injury" and physical and mental pain and suffering." *See* Petition, ¶14.

11.

Based on plaintiff's stated claims, it is clear that the amount in controversy is in excess of $75,000.00, exclusive of interests and costs.

Consent

12.

Schwarz and Actavis have joined in and consented to this removal. *See* Exhibits "C" and "D."

Other Matters

13.

Pursuant to 28 U.S.C. §1446, a copy of this Notice of Removal is being filed with the Clerk for the 22nd Judicial District Court for the Parish of St. Tammany, State of Louisiana.

14.

Wyeth reserves the right to amend or supplement this Notice of Removal.

15.

This action is removable pursuant to 28 U.S.C. §1441(a) because Wyeth is removing this action to the District Court of the United States for the district and division embracing the place where the action is pending.

16.

Wyeth requests trial by jury of all issues.

WHEREFORE, Petitioner Wyeth hereby removes the action now pending against it in the 22nd Judicial District Court for the Parish of St. Tammany, State of

Louisiana, bearing docket number 2008-12332, to this Honorable Court.

Respectfully submitted,

/s/ Ann R. Koppel

MARTIN A. STERN, #17154, T.A.
ANN R. KOPPEL, #27252
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A Professional Limited Liability Partnership
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Attorneys for Defendant, Wyeth

[*Certificate of Service omitted in printing of this appendix*]

* * *

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA

CIVIL ACTION
NO. _____

SECTION _____

JULIE DEMAHY	)
	)
VERSUS	)
	)
WYETH, INC. D/B/A WYETH, INDIVIDUALLY AND AS SUCCESSSOR IN INTEREST OF A.H. ROBINS COMPANY, INC., SCHWARZ PHARMA, INC., AND ACTAVIS INC., INDIVIDUALLY AND AS SUCCESSOR IN INTEREST OF PUREPAC PHARMACEUTICAL CO.	)

CERTIFICATE OF FILING NOTICE OF REMOVAL IN STATE COURT

JURY TRIAL REQUESTED

The undersigned counsel for Defendant Wyeth hereby certify that they will file with the Clerk of the Twenty-Second Judicial District Court for the Parish of St. Tammany, State of Louisiana, a Notice of Filing Notice of Removal, along with a copy of Defendant's Notice of Removal, and the original Citation and Petition in the Action in said court.

Respectfully submitted,

/s/ Ann R. Koppel

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ANN R. KOPPEL, #27252
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A Professional Limited Liability Partnership
4500 One Shell Square
New Orleans, LA 70139
Telephone: (504) 581-3234

Attorneys for Defendant, Wyeth

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF LOUISIANA

CIVIL ACTION NO. 08-3616

SECTION: "J" (2)

JUDGE: CJB/JCW

[Filed June 6, 2008]

JULIE DEMAHY,	)
Plaintiff,	)
v.	)
	)
WYETH, INC., *et al.*,	)
Defendants.	)
	)

ANSWER OF DEFENDANT ACTAVIS, INC.
JURY TRIAL DEMANDED

For its Answer to the Petition for Damages ("Petition") of Plaintiff Julie Demahy ("Plaintiff"), Defendant Actavis, Inc. ("Actavis") states as follows:

ANSWER TO INTRODUCTORY COMMENTS

To the extent the statements which appear before Paragraph 1A of the Petition can be construed to contain any substantive allegations, Actavis denies the allegations contained therein.

1. Actavis is without knowledge or information sufficient to form a belief as to the truth of the allegations contained in Paragraphs 1A and 1B of the

Petition and, therefore, denies the allegations contained in Paragraphs 1A and 1B of the Petition. Actavis denies the allegations contained in Paragraph 1C of the Petition. Further answering, Actavis states that its subsidiary, Actavis-Elizabeth, LLC, is the successor to Purepac Pharmaceutical Co. Further answering, Actavis admits United Corporate Services, Inc. is its registered agent for purposes of receiving service in the State of Delaware. Actavis denies all remaining allegations in Paragraph 1C of the Petition.

2. Actavis denies the allegations contained in Paragraph 2 of the Petition.

3. In response to the allegations contained in Paragraph 3 of the Petition, Actavis states that Purepac Pharmaceutical Co. manufactured and distributed Metoclopramide, denies all allegations contained in Paragraph 3 of the Petition directed at Actavis, and is without knowledge or information sufficient to form a belief as to the truth of the remaining allegations contained in Paragraph 3 of the Petition and, therefore, denies the remaining allegations contained in Paragraph 3 of the Petition.

4. In response to the allegations contained in Paragraph 4 of the Petition, Actavis states that Purepac Pharmaceutical Co. manufactured and distributed Metoclopramide, denies all allegations contained in Paragraph 4 of the Petition directed at Actavis, and is without knowledge or information sufficient to form a belief as to the truth of the remaining allegations contained in Paragraph 4 of the Petition and, therefore, denies the remaining allegations contained in Paragraph 4 of the Petition.

5. In response to the allegations contained in Paragraph 5 of the Petition, Actavis states that Purepac Pharmaceutical Co. manufactured and distributed Metoclopramide, denies all allegations contained in Paragraph 5 of the Petition directed at Actavis, and is without knowledge or information sufficient to form a belief as to the truth of the remaining allegations contained in Paragraph 5 of the Petition and, therefore, denies the remaining allegations contained in Paragraph 5 of the Petition.

6. In response to the allegations contained in Paragraph 6 of the Petition, Actavis states that Purepac Pharmaceutical Co. manufactured and distributed Metoclopramide, denies all allegations contained in Paragraph 6 of the Petition directed at Actavis, and is without knowledge or information sufficient to form a belief as to the truth of the remaining allegations contained in Paragraph 6 of the Petition and, therefore, denies the remaining allegations contained in Paragraph 6 of the Petition.

7. Actavis denies the allegations contained in Paragraph 7 of the Petition.

8. Actavis is without knowledge or information sufficient to form a belief as to the truth of the allegations contained in Paragraph 8 of the Petition and, therefore, denies the allegations contained in Paragraph 8 of the Petition.

9. Actavis is without knowledge or information sufficient to form a belief as to the truth of the allegations contained in Paragraph 9 of the Petition and, therefore, denies the allegations contained in Paragraph 9 of the Petition.

10. Actavis is without knowledge or information sufficient to form a belief as to the truth of the allegations contained in Paragraph 10 of the Petition and, therefore, denies the allegations contained in Paragraph 10 of the Petition.

11. The allegations contained in Paragraph 11 of the Petition are definitional and require no response.

12. In response to the allegations contained in Paragraph 12 of the Petition, Actavis admits that Metoclopramide has the pharmacological effects set forth in the FDA-approved package insert. Actavis denies the remaining allegations in Paragraph 12 of the Petition, and denies it ever has manufactured or distributed Metoclopramide.

13. In response to the allegations contained in Paragraph 13 of the Petition, Actavis denies that Metoclopramide caused any injury to Plaintiff, and is without knowledge or information sufficient to form a belief as to the truth of the remaining allegations in Paragraph 13 of the Petition and, therefore, denies the remaining allegations contained in Paragraph 13 of the Petition.

14. In response to the allegations contained in Paragraph 14 of the Petition, Actavis denies that Metoclopramide caused any injury to Plaintiff, and is without knowledge or information sufficient to form a belief as to the truth of the remaining allegations in Paragraph 14 of the Petition and, therefore, denies the remaining allegations contained in Paragraph 14 of the Petition.

15. Actavis denies the allegations contained in Paragraph 15 of the Petition.

16. In response to the allegations contained in Paragraph 16 of the Petition, Actavis admits that the indicated use in the package insert approved for Metoclopramide by the Food and Drug Administration does not exceed 12 weeks. Actavis denies the remaining allegations contained in Paragraph 16 of the Petition.

17. Actavis denies the allegations contained in Paragraph 17 of the Petition.

18. In response to the allegations contained in Paragraph 18 of the Petition, Actavis denies all allegations relating to Actavis and is without knowledge or information sufficient to form a belief as to the truth of the remaining allegations contained in Paragraph 18 of the Petition and, therefore, denies the remaining allegations contained in Paragraph 18 of the Petition.

19. In response to the allegations contained in Paragraph 19 of the Petition, Actavis denies that it ever has manufactured or distributed Metoclopramide. Further answering, Actavis admits that manufacturers of generic drugs have a duty to comply with FDA regulations and are required by such regulations to use exactly the same warning label approved for the brand-name manufacturer. Actavis is without knowledge or information sufficient to form a belief as to the truth of the remaining allegations contained in Paragraph 19 of the Petition and, therefore, denies the remaining allegations contained in Paragraph 19 of the Petition.

20. Actavis denies the allegations contained in Paragraph 20 of the Petition.

21. In response to the allegations contained in Paragraph 21 of the Petition, Actavis denies that it ever has manufactured or distributed Metoclopramide. Further answering, Actavis admits that manufacturers of generic drugs have a duty to comply with FDA regulations and are required by such regulations to use exactly the same warning label approved for the brand-name manufacturer. Actavis is without knowledge or information sufficient to form a belief as to the truth of the remaining allegations contained in Paragraph 21 of the Petition and, therefore, denies the remaining allegations contained in Paragraph 21 of the Petition.

22. Actavis denies the allegations contained in Paragraph 22 of the Petition.

23. Actavis denies the allegations contained in Paragraph 23 of the Petition.

24. Actavis denies the allegations contained in Paragraph 24 of the Petition.

25. Actavis denies the allegations contained in Paragraph 25 of the Petition.

26. Actavis denies the allegations contained in Paragraph 26 of the Petition.

27. The allegations contained in Paragraph 27 of the Petition do not refer to Actavis, and therefore no response is required.

28. Actavis denies the allegations contained in Paragraph 28 of the Petition.

29. Actavis denies the allegations contained in Paragraph 29 of the Petition.

30. Actavis denies the allegations contained in Paragraph 30 of the Petition.

31. Actavis denies the allegations contained in Paragraph 31 of the Petition.

32. Actavis denies the allegations contained in Paragraph 32 of the Petition.

33. Actavis denies the allegations contained in Paragraph 33 of the Petition.

34. Actavis denies the allegations contained in Paragraph 34 of the Petition.

35. Actavis denies the allegations contained in Paragraph 35 of the Petition.

36. Actavis denies the allegations contained in Paragraph 36 of the Petition.

37. Actavis denies the allegations contained in Paragraph 37 of the Petition.

38. Actavis denies the allegations contained in Paragraph 38 of the Petition.

39. Actavis denies all allegations contained in Paragraph 39 of the Petition directed at Actavis, and is without knowledge or information sufficient to form

a belief as to the truth of the remaining allegations contained in Paragraph 39 of the Petition and, therefore, denies the remaining allegations contained in Paragraph 39 of the Petition.

40. In response to the allegations contained in Paragraph 40 of the Petition, Actavis denies that Metoclopramide caused any injury to Plaintiff, denies all allegations contained in Paragraph 40 directed at Actavis, and is without knowledge or information sufficient to form a belief as to the truth of the remaining allegations contained in Paragraph 40 of the Petition and, therefore, denies the remaining allegations contained in Paragraph 40 of the Petition.

41. Actavis denies the allegations contained in Paragraph 41 of the Petition.

42. Actavis denies the allegations contained in Paragraph 42 of the Petition.

43. Actavis denies the allegations contained in Paragraph 43 of the Petition.

44. In response to the allegations in Paragraph 44 of the Petition, Actavis states that Metoclopramide is a pharmaceutical product determined to be safe and effective by the Federal Food & Drug Administration. Further answering, this Defendant denies all the remaining allegations in Paragraph 44.

45. Actavis denies the allegations contained in Paragraph 45 of the Petition.

46. Actavis denies the allegations contained in Paragraph 46 of the Petition.

47. Actavis denies the allegations contained in Paragraph 47 of the Petition.

48. Actavis denies the allegations contained in Paragraph 48 of the Petition.

49. Actavis denies the allegations contained in Paragraph 49 of the Petition.

50. Actavis denies the allegations contained in Paragraph 50 of the Petition.

51. Actavis denies the allegations contained in Paragraph 51 of the Petition.

52. Actavis specifically controverts the prayer for relief set forth below Paragraph 51 of the Petition.

53. Actavis denies each and every allegation of Plaintiff's Petition not heretofore specifically admitted in this Answer.

Furthermore, Actavis asserts the following Affirmative Defenses:

FIRST DEFENSE

54. Plaintiff's Petition fails to state a claim upon which relief may be granted.

SECOND DEFENSE

55. Actavis affirmatively states that any Metoclopramide sold by Actavis was appropriately designed and manufactured, was accompanied by appropriate warnings, was not defective or

unreasonably dangerous, was not negligently designed or manufactured, and that Actavis did not breach any warranties.

THIRD DEFENSE

56. Actavis adopts and incorporates by reference as if fully set out herein any and all defenses which are or may become available to it under the Louisiana Products Liability Act, LSA – R.S. 9:2800.51, *et seq*.

FOURTH DEFENSE

57. Actavis adopts and incorporates by reference as if fully set out herein any and all defenses which are or may become available to it under the Uniform Commercial Code as adopted in Louisiana, LSA – R.S. 10:1-101, *et seq*..

FIFTH DEFENSE

58. Actavis adopts and incorporates by reference as if fully set out herein any and all defenses which are or may become available to it under the *Restatement (Second) of Torts*, § 402A and all comments thereto and the *Restatement (Third) of Torts*, §§ 1-21 and all comments thereto.

SIXTH DEFENSE

59. All or part of the claims in this action may be barred by Actavis' compliance with all statutory and regulatory requirements.

SEVENTH DEFENSE

60. All or part of the claims in this action may be barred by Plaintiff's assumption of risk of her alleged injuries and damages.

EIGHTH DEFENSE

61. All or part of the claims in this action may be barred by the learned intermediary doctrine.

NINTH DEFENSE

62. All or part of the claims in this action may be barred by the doctrine of federal preemption.

TENTH DEFENSE

63. The injuries complained of may have been caused by an idiosyncratic reaction.

ELEVENTH DEFENSE

64. All or part of the claims in the Petition may be barred by the applicable statutes of limitation.

TWELFTH DEFENSE

65. The claims in the Petition fail to comply with the requirements of Rule 9(b) of the Federal Rules of Civil Procedure.

THIRTEENTH DEFENSE

66. All or part of the damages alleged in the Petition may have been caused by the negligence or fault of Plaintiff.

FOURTEENTH DEFENSE

67. The claim for joint liability fails to state a claim upon which relief can be granted.

FIFTEENTH DEFENSE

68. To the extent that Plaintiff seeks punitive damages for the conduct which allegedly caused injuries asserted in the Petition, punitive damages are barred or reduced by applicable law or statute or, in the alternative, are unconstitutional insofar as they violate the due process protections afforded by the United States Constitution, the excessive fines clause of the Eighth Amendment of the United States Constitution, the Commerce Clause of the United States Constitution, the Full Faith and Credit Clause of the United States Constitution, and applicable provisions of the Constitution of the State of Louisiana. Any law, statute, or other authority purporting to permit the recovery of punitive damages in this case is unconstitutional, facially and as applied, to the extent that, without limitation, it: (1) lacks constitutionally sufficient standards to guide and restrain the jury's discretion in determining whether to award punitive damages and/or the amount, if any; (2) is void for vagueness in that it failed to provide adequate advance notice as to what conduct will result in punitive damages; (3) permits recovery of punitive damages based on out-of-state conduct, conduct that complied

with applicable law, or conduct that was not directed, or did not proximately cause harm to Plaintiff; (4) permits recovery of punitive damages in an amount that is not both reasonable and proportionate to the amount of harm, if any, to Plaintiff and to the amount of compensatory damages, if any; (5) permits jury consideration of net worth or other financial information relating to this Defendant; (6) lacks constitutionally sufficient standards to be applied by the trial court in post-verdict review of any punitive damages awards; (7) lacks constitutionally sufficient standards for appellate review of punitive damages awards; and (8) otherwise fails to satisfy Supreme Court precedent.

SIXTEENTH DEFENSE

69. In the absence of proof by Plaintiff that the product used and ingested by Plaintiff was made or distributed by Actavis, Actavis may not be held liable for any claim herein.

SEVENTEENTH DEFENSE

70. Plaintiff's Petition is barred for failure to join indispensable parties.

EIGHTEENTH DEFENSE

71. Plaintiff's recovery, if any, should be reduced pursuant to the comparative negligence, fault, responsibility, or causation of others.

NINETEENTH DEFENSE

72. Plaintiff's alleged damages were caused by her failure to exercise ordinary care to follow the advice, information, warnings, and instructions provided with any product marketed by Actavis.

TWENTIETH DEFENSE

73. Plaintiff's alleged injuries and damages, if any, were the result of the misuse of the subject pharmaceutical product at issue. Actavis further alleges that if Plaintiff suffered injuries attributable to Plaintiff's use of the subject pharmaceutical product at issue in this suit, which allegations are expressly denied, the injuries, if any, were solely caused and attributable to the unreasonable, unforeseeable, and improper use of said pharmaceutical product by Plaintiff and/or third parties.

TWENTY-FIRST DEFENSE

74. Plaintiff's alleged damages were caused by the negligence or other fault of persons or entities other than Actavis who are not within the control of Actavis and for whom Actavis has no liability.

TWENTY-SECOND DEFENSE

75. Plaintiff's alleged damages resulted from new and independent, unforeseeable, superseding and/or intervening causes unrelated to any conduct of, or product placed in the stream of commerce by, Actavis.

TWENTY-THIRD DEFENSE

76. Plaintiff's alleged damages were the result of preexisting conditions unrelated to any conduct of, or product placed in the stream of commerce by, Actavis.

TWENTY-FOURTH DEFENSE

77. Reglan® and/or generic Metoclopramide was designed, tested, manufactured, and marketed in conformance with the state of the scientific, medical, and technological art and knowledge existing at the time of sale and, accordingly, Plaintiff's claims are barred.

TWENTY-FIFTH DEFENSE

78. Plaintiff's claims are barred in whole or in part because there is no private right of action concerning matters regulated by the Food and Drug Administration under applicable federal laws, regulations, and rules.

TWENTY-SIXTH DEFENSE

79. The pharmaceutical product at issue was fit and proper for its intended purpose and the utility of the subject pharmaceutical product at issue outweighs any possible risk inherent in the use of the subject pharmaceutical product.

TWENTY-SEVENTH DEFENSE

80. Actavis is informed and believes and thereon alleges that Plaintiff failed to provide Actavis with

timely notice of any alleged nonconformance with any express representation.

TWENTY-EIGHTH DEFENSE

81. Plaintiff's claims are barred because Plaintiff would have taken the subject pharmaceutical product even if the subject pharmaceutical product's labeling contained the information that Plaintiff contends should have been provided.

TWENTY-NINTH DEFENSE

82. Plaintiff's claims are barred, in whole or in part, because the advertisements, if any, and labeling with respect to the subject pharmaceutical product were not false or misleading and, therefore, constitute protected commercial speech under the applicable provisions of the United States Constitution.

THIRTIETH DEFENSE

83. Actavis made no warranties of any kind, express or implied, or any representations of any nature whatsoever to Plaintiff. Additionally, as a manufacturer and not a seller, Actavis is not subject to liability for implied warranties without privity, i.e., proof of direct and specific transactions between Plaintiff and, Actavis. If any such warranties were made, whether express or implied, which Actavis specifically denies, then Plaintiff failed to give timely notice of any breach thereof.

THIRTY-FIRST DEFENSE

84. Neither Plaintiff nor Plaintiff's respective physicians were induced to prescribe or use Reglan® and/or generic Metoclopramide based on any material representations or misrepresentations of Actavis.

THIRTY-SECOND DEFENSE

85. Plaintiff did not rely on any express or implied warranty allegedly made by Actavis.

THIRTY-THIRD DEFENSE

86. Plaintiff's alleged damages were caused in whole or in part by Plaintiff's failure to mitigate such damages.

THIRTY-FOURTH DEFENSE

87. Plaintiff's causes of action may be barred, in whole or in part, by the equitable doctrines of laches, waiver, and estoppel.

THIRTY-FIFTH DEFENSE

88. Plaintiff impermissibly seeks to impose liability on conduct protected from liability by the First Amendment to United States Constitution.

THIRTY-SIXTH DEFENSE

89. Actavis reserves the right to amend this Answer to raise any and all defenses, affirmative or otherwise, which may become available to it during the course of this action.

WHEREFORE, having fully answered, Actavis prays that Plaintiff's Petition for Damages be dismissed, with prejudice, that judgment be granted in favor of Actavis on all claims asserted in Plaintiff's Petition for Damages, and that Actavis be granted its costs, expenses, interest, reasonable attorneys fees, and such other legal and equitable relief as this Court deems proper in the circumstances.

Lemle & Kelleher, L.L.P.

/s/ Elizabeth Haecker Ryan
Elizabeth Haecker Ryan (LA Bar #6404)
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Telephone: 504.584.9138
Facsimile: 504.584.9142
Email: eryan@lemle.com

Attorneys for Defendant Actavis, Inc.

JURY DEMAND

Pursuant to Rule 38(b) of the Federal Rules of Civil Procedure, Defendant Actavis, Inc. hereby respectfully requests a trial by jury, composed of the maximum number of jurors allowed by law, on all issues triable to a jury in this matter.

Lemle & Kelleher, L.L.P.

/s/ Elizabeth Haecker Ryan
Elizabeth Haecker Ryan (LA Bar #6404)
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Attorneys for Defendant Actavis, Inc.

[Certificate of Service omitted in printing of this appendix]

* * *

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA

CIVIL ACTION

NO: 08-3616

SECTION: J

[Filed October 28, 2008]

JULIE DEMAHY	)
	)
VERSUS	)
	)
WYETH INC., ET AL	)
	)

ORDER & REASONS

Before the Court is Defendant Actavis Inc.'s ("Actavis") **Motion to Dismiss (Rec. Doc. 19)** under Rule 12(b)(6) based on federal conflict preemption. The motion came before the Court for oral argument on September 17, 2008, and was taken under advisement. Having reviewed the motion, the memoranda of counsel, the parties' statements at oral argument, and the applicable law, the Court finds as follows.

FACTS & PROCEDURAL HISTORY

Plaintiff Julie Demahy ("Demahy"), a fifty-eight year old female, began taking metoclopramide, the generic version of the name brand drug Reglan, in 2002 and continued treatment until April 2006. Metoclopramide is prescribed for treatment of

gastroesophagal reflux disease, commonly known as acid reflux. In October of 2007, Demahy was diagnosed by physicians at the University of Texas, Southwestern Medical Center with tardive dyskenesia, which the doctors believed had been caused by long-term use of metoclopramide. Tardive dyskenesia is a neurological disorder that causes involuntary movements of the face, torso, and extremities.

As a result of her injuries allegedly caused by her treatment with metoclopramide, Demahy filed suit against Wyeth Inc., Schwarz Pharma, Inc., and Actavis in the 22nd Judicial District Court for the Parish of St. Tammany. In her state court complaint, Demahy asserted personal injury claims under the Louisiana Products Liability Act ("LPLA"), specifically for failure to warn of the risks of neurological disorder after long-term use of metoclopramide. In addition, Demahy claims that Actavis breached its duty to provide updated information regarding the hazards of metoclopramide to the Food and Drug Administration ("FDA"), which would have resulted in more adequate warnings on the labels for the drug. Further, Demahy claims that Actavis intentionally concealed scientific research regarding the risks of metoclopramide with respect to neurological disorders in order to mislead the medical community and prevent FDA action.

The case was removed to this Court on June 6, 2008 (Rec. Doc. 1). Defendants Wyeth, Inc. and Schwarz Pharma, Inc. have been dismissed from the suit without prejudice (Rec. Doc. 15). Thus, only defendant Actavis remains. Actavis, formerly Purepak Pharmaceutical Company, is a generic manufacturer of metoclopramide, and according to Demahy's pharmacy records was the manufacturer of the

metoclopramide she consumed. The parties do not dispute that Actavis's label and package insert for its generic metoclopramide was at all relevant times identical to the label and package insert for the name brand drug.

THE PARTIES' ARGUMENTS

Actavis argues that Demahy's products liability claims under the LPLA should be dismissed as a matter of federal conflict preemption. Specifically, Actavis asserts that under the relevant provisions of the Food, Drug, and Cosmetics Act ("FDCA"), the label and package insert for its generic product need not and in fact could not have been altered from the label and package insert that was approved by the FDA for name brand metoclopramide. As such, Actavis argues that Demahy's LPLA failure-to-warn claims are preempted both as a matter of direct conflict preemption, since Actavis's failure-to-warn duties under the LPLA directly conflict with its duties to maintain identical labels under the FDCA, and as a matter of so-called "obstacle preemption," since compliance with failure-to-warn tort principles under the LPLA would frustrate the goals of the FDCA and the 1984 Hatch-Waxman Amendments to the FDCA.

The Hatch-Waxman Amendments provided differing approval standards for generic drug manufacturers from those applicable to name brand drug manufacturers. See 21 U.S.C. § 355(j) (2008). According to Actavis, the Hatch-Waxman Amendment codified FDA regulations in order to streamline generic drug approval and eliminate the need for generic manufacturers to replicate the time-consuming and costly drug safety research already performed by the

name brand manufacturer. The truncated process by which a generic drug is approved is referred to in §355(j) as an Abbreviated New Drug Application ("ANDA") as opposed to the more extensive New Drug Application ("NDA") required for name brand drugs. Under the ANDA process, Actavis asserts that generic drugs are not subject to the same initial and continuing testing and reporting requirements as name brand drugs. Additionally, according to Actavis, the FDA mandates that generic drug labels must *always* remain identical to the FDA-approved labels of the pioneer name brand drug. See §355(j)(2)(A)(v). As such, Actavis argues that the FDA has specifically rejected the availability to generic drug manufacturers of the Changes Being Effected ("CBE") mechanism provided in 21 C.F.R. §314.70, which allows name-brand drug manufacturers to make unilateral post-approval labeling changes, subject to FDA notice and approval. Accordingly, Actavis asserts that Demahy's LPLA claims are preempted because any state law duty to alter or increase generic drug label warnings over and above the labeling approved by the FDA conflicts with the requirements and goals of the FDCA and applicable regulations.

In opposition, Demahy claims that the §355(j) ANDA labeling requirements apply only during the *initial approval* process for a generic drug. After a generic drug has been approved by the FDA via the ANDA process, however, Demahy asserts that the generic manufacturer has a continuing duty under the LPLA and the FDCA to include warnings regarding newly discovered risks "as soon as there is reasonable evidence of a causal association with a drug." 21 C.F.R. §§201.57(c)(6)(I) & 201.80(e).

Demahy argues further that while it is "questionable" whether generic manufacturers can utilize the CBE procedures under 21 C.F.R. §314.70 to unilaterally add new safety information to their labels, Actavis still had some duty to at least notify the FDA of possible adverse side effects. Thus, because Actavis essentially did nothing, it should be liable under the LPLA for failure to warn of the adverse neurological side effects of metoclopramide that allegedly caused Demahy's tardive dyskinesia.

In response, Actavis reiterates that generic drug labels must always remain identical to those of the name brand drug. Also, Actavis argues that the regulations relied on by Demahy regarding the duty to update labels are inapplicable to generic drug manufacturers.

LAW & DISCUSSION

As set forth by the Supreme Court in Bell Atlantic Corp. v. Twombly, 127 S. Ct. 1955 (2007), the standard to be applied when deciding a Rule 12(b)(6) motion is not whether it is conceivable that some set of facts could be developed to support the allegations in the complaint, but rather whether the plaintiffs have stated enough facts in the complaint to allow a court to conclude that it is "plausible" that the plaintiffs are entitled to relief. The Court must accept as true all well-plead allegations and resolve all doubts in favor of the plaintiff. Tanglewood East Homeowners v. Charles-Thomas, Inc., 849 F.2d 1568, 1572 (5th Cir. 1988).

As a preliminary matter, it should be noted that Demahy's claims are preempted to the extent they

allege fraud-on-the-FDA under state law with regard to Actavis's alleged intentional concealment of medical research concerning the neurological effects of metoclopramide. See Buckman Co. v. Pl.'s Legal Comm., 531 U.S. 341, 348 (2001) (holding that "state law fraud-on-the-FDA claims conflict with, and are therefore impliedly pre-empted by, federal law"). Therefore, any fraud-on-the-FDA claim by Demahy under Louisiana law is preempted and must be dismissed under Rule 12(b)(6) for failure to state a cause of action.

A. Federal Conflict Preemption

Actavis asserts that Demahy's LPLA failure-to-warn claims are barred as a matter of implied federal conflict preemption[1] under the FDCA and applicable interpretive regulations and other position documents of the FDA.

The principles of implied conflict preemption proceed from the Supremacy Clause of the United States Constitution, and provide that federal law must prevail over state law when "it is **impossible** for a private party to comply with both state and federal requirements or where state law stands as an **obstacle** to the accomplishment and execution of the full purposes and objectives of Congress." Freightliner Corp. v. Myrick, 514 U.S. 280, 287 (1995) (internal quotations and citations omitted) (emphasis added).

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[1] The parties do not dispute the fact that the FDCA itself does not expressly preempt state law failure-to-warn claims against generic drug manufacturers. Therefore only implied conflict preemption is at issue.

Conflict preemption is "fundamentally a question of congressional intent," as opposed to instances of express preemption in which Congress enacts a statute that expressly provides for preemption of state law. Geier v. Am. Honda Motor Co., 529 U.S. 861, 884 (2000). As such, analysis of implied federal conflict preemption should proceed from a "presumption against pre-emption [sic]" when a case concerns whether state authority conflicts with the existence of federal authority. New York v. F.E.R.C., 535 U.S. 1, 17-18 (2002). Thus when federal authority is at odds with state law, a court must "start with the assumption that the historic police powers of the States," such as health and safety regulation, "were not to be superseded . . . unless that was the clear and manifest purpose of Congress." Hillsborough County, Fl. v. Automative Med. Labs., Inc., 471 U.S. 707, 715 (1985).

B. Agency Interpretations and Judicial Deference

When a court reviews an agency's construction of a statute that it administers, the court must determine "whether Congress has directly spoken to the precise question at issue," for if Congressional intent is clear, both "the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress." Chevron U.S.A., Inc. v. Natural Res. Def. Council, Inc., 467 U.S. 837, 842-43 (1984). However, "if the statute is silent or ambiguous with respect to the specific issue," the court must determine "whether the agency's construction is based on a permissible construction of the statute." Id. at 843. On these terms, agency regulations are controlling "unless they are arbitrary, capricious, or manifestly contrary to the statute." Id. at

844. Under these broad principles, the Supreme Court has developed three different deference analyses for specific types of agency actions.

1) Chevron Deference

Besides the process of enacting administrative regulations, however, administrative agencies "necessarily make all sorts of interpretive choices, and while not all of those choices bind judges to follow them, they certainly may influence courts facing questions the agencies have already answered." United States v. Mead Corp., 533 U.S. 218, 227 (2001). Nonetheless, "[t]he fair measure of deference to an agency administering its own statute has been understood to vary with the circumstances, and courts have looked to the degree of the agency's care, its consistency, formality, and relative expertness, and to the persuasiveness of the agency's position." Id. at 228 (citations omitted). In this analysis, "the fact that the agency has from time to time changed its interpretation . . . does not . . . lead [to the conclusion] that no deference should be accorded the agency's interpretation of the statute." Chevron, 467 U.S. at 863-64. Additionally, under the Court's holding in Chevron, when Congress has generally conferred authority on an agency, Congress expects the agency to speak with the binding authority of law "when it addresses ambiguity in the statute or fills a space in the enacted law," even if there was no congressional intent for a particular result. Mead Corp., 533 U.S. at 229. In this regard, "[i]t is fair to assume that Congress contemplates administrative action with the effect of law when it provides for a relatively formal administrative procedure tending to foster the fairness and deliberation that should underlie a pronouncement

of such force." Id. Accordingly, most cases in which courts have afforded the high level of Chevron deference to agency statements have involved only the results of notice-and-comment rulemaking, namely regulations, or formal adjudications. Id. at 230. Nonetheless, the Court has occasionally afforded Chevron deference to unofficial agency interpretations depending on the circumstances, but only when the agency's interpretation is "reasonable" and when the authorization and procedure for promulgating the interpretation evidences congressional intent that it be binding. Meade, 533 U.S. at 229-31.

2) Auer Deference

In addition to this high Chevron standard of deference, the Supreme Court has developed a second standard of deference when the language of the regulation is ambiguous. An agency's interpretation of its own ambiguous regulation is entitled to deference unless it is "plainly erroneous or inconsistent with the regulation" being interpreted. Auer v. Robbins, 519 U.S. 452, 461 (1997) (internal quotation marks omitted). As such, the Fifth Circuit employs a two step test when interpreting an agency regulation: 1) whether the regulation is "ambigu[ous] **with respect to the specific question considered**," and 2) whether the agency's interpretation of its ambiguous regulation is "plainly erroneous or inconsistent with the regulation." Belt v. EmCare, Inc., 444 F.3d 403, 408 (5th Cir. 2006) (citing Christensen v. Harris County, 529 U.S. 576, 588, (2000) & Auer, 519 U.S. at 461) (emphasis added).

3) Skidmore Deference

Finally, in addition to Chevron and Auer deference, the Court has developed the third and least deferential Skidmore standard for situations in which an agency lacks the congressional authority required for Chevron deference and the regulation at issue is not ambiguous, thus precluding Auer deference. This Skidmore standard provides that an agency's "rulings, interpretations, and opinions" are not controlling on courts, but merely "constitute a body of experience and informed judgment to which courts and litigants may properly resort for guidance." Skidmore v. Swift & Co., 323 U.S. 134, 140 (1944). As such, an agency's informal position statements are subject to "some weight" and should "make a difference" in a court's preemption analysis. See Geier, 529 U.S. at 883. Nonetheless, the weight of deference under Skidmore is affected by "the thoroughness evident in its consideration, the validity in its reasoning, its consistency with earlier and later pronouncements, and all those factors which give it power to persuade, if lacking power to control." Skidmore, 323 U.S. at 140. Essentially, under Skidmore a court merely considers whether the agency statement at issue has the "power to persuade." Id.

Along with the development of these three differing standards of deference, the Supreme Court has held that an agency's preemption interpretations of the statutes it is authorized to implement may be entitled to some level of deference. Geier, 529 U.S. at 883 (noting that Department of Transportation's comments supporting the preemptive affect of its Federal Motor Vehicle Safety Standard promulgated under the National Traffic and Motor Vehicle Safety Act should "make a difference" in the Court's conflict preemption

analysis). In fact, the Court has held that federal regulations, as well as federal statutes, can themselves preempt state law. Hillsborough, 471 U.S. at 713.

C. The FDA's Position on Preemption of State Law Failure-to-Warn Claims under the FDCA.

Actavis has pointed the Court to five specific pieces of evidence that support its position that the FDCA, applicable regulations, and informal FDA position statements have consistently over the past twenty years supported the proposition that state law failure-to-warn claims based on the inadequacy of generic drug labels are preempted as matter of conflict preemption. Each of these pieces of evidence will be treated in succession.

1) Abbreviated New Drug Application Regulations, 54 Fed Reg 28872, 28884 (proposed July 10, 1989) (hereinafter "1989 Proposed Rule")

The first piece of evidence Actavis cites stems from the proposed rule and comments created during the FDA's initial rulemaking process to implement the provisions of the 1984 Hatch-Waxman amendments. See 1989 Proposed Rule at 28872 ("[FDA] is proposing regulations to implement [the Hatch-Waxman amendments]"). The proposed rules were intended to "benefit consumers by making generic drug products available more quickly." Id. The relevant portion of the 1989 Proposed Rule cited by Actavis provides the following:

> In addition, the act requires that an applicant include in the ANDA information adequate to

show that the proposed labelling [sic] for its drug product is the same as that of the reference listed drug except for changes required because of differences approved under a petition or because the drug product and the reference listed drug are produced or distributed by different manufacturers.

. . .

FDA emphasizes that the exceptions to the requirement that a generic drug's labeling be the same as that of the listed drug are limited. The agency will not accept ANDA's for products with significant changes in labeling (such as new warnings or precautions) intended to address newly introduced safety or effectiveness problems not presented by the listed drug. Such labeling changes do not fall within the limited exceptions in sections 505(j)(2)(A)(v) and 505(j)(3)(G) of the act. Moreover, FDA does not believe that it would be consistent with the purpose of section 505(j) of the act, which is to assure the marketing of generic drugs that are as safe and effective as their brand-name counterparts, to interpret section 505(j)(2)(A)(v) of the act as permitting the marketing of generic drugs with diminished safety or effectiveness and concomitantly heightened labeled warnings. Thus, where a proposed change in a generic drug, e.g., in packaging or inactive ingredients or, for a petition-approved drug, in the approved change, would jeopardize the safe or effective use of the product so as to necessitate the addition of significant new labeled warnings, the proposed product would not satisfy the labeling requirements of sections 505(j)(2)(A)(v) and 505(j)(3)(G) of the act.

> To assist the agency in determining if the applicant's proposed labeling is the "same as" that of the reference listed drug, except for the types of differences described above, FDA proposes in § 314.94(a)(8)(iv) to require the applicant to include in the ANDA a side-by-side comparison of the applicant's proposed labeling with the currently approved labeling for the listed drug referred to in the ANDA with all differences annotated and explained.

Id. at 28884.

Actavis cites the above quoted portion of the 1989 Proposed Rule for the proposition that "[f]or almost twenty years, the FDA has consistently stated that generic labeling must, **at all times be identical** to name brand labeling and that only it, alone, may determine whether generic labeling should be revised." Def.'s Reply Mem. Supp. Sum. J., 1 (emphasis added). However, the 1989 Proposed Rule does not address the question of whether generic labels must **always** be identical to that of the name brand pioneer drug; rather, the 1989 Proposed Rule concerns **only the initial ANDA application and approval process**, and thus only concerns whether the generic label must be the same as the name brand at the time of the initial ANDA application. See generally 1989 Proposed Rule at 2875-76. Neither party disputes the fact that a generic drug must have the "same" label as the name brand pioneer drug at the time of an initial ANDA application. The crucial question, which the 1989 Proposed Rule does not address, is whether a generic drug *that has already been approved* via the ANDA process can change its label to include new or different

warnings without FDA approval. Thus Actavis's reference to the 1989 Proposed Rule merely begs the question at issue in this case of whether a generic drug manufacturer can update its labels to comply with state law tort duties after initial FDA approval without violating the FDCA.

Furthermore, it is interesting to note that from the very beginning, the FDA has required that ANDA applicants include labels that are the "same" as those approved for the name brand pioneer drug. The 1989 Proposed Rule makes numerous references to this "same as" requirement. On the other hand, the FDA's regulation that specifically applies to *withdrawal* of generic drug approvals after the initial ANDA approval provides that an such approval can be withdrawn if the label for the generic is "no longer **consistent with** that for the listed drug." 21 C.F.R. §314.150(b)(1)(2008). If the FDA truly intended generic drug labels to be the "same as" the name brand drug labels throughout the life of the generic drug, the discrepancy between the manifold use of the phrase "same as" in the FDA's initial rulemaking on the *pre-approval* ANDA process is curious in comparison to the use of the phrase "consistent with" in the regulation governing *post-approval* processes. Further implications of 21 C.F.R. §314.150 with respect to Actavis's preemption arguments are discussed in section C(3) below.

Finally, the 1989 Proposed Rule itself contemplates approval of post-ANDA unilateral labeling changes by generic drug manufacturers. In discussing the different procedural protections that must be afforded to NDA and ANDA approved manufacturers during the approval withdrawal process, the FDA commented:

> The agency recognizes, however, that ANDA holders may be entitled to more extensive procedural protections when the agency proposes to withdraw approval of their applications under sections 505(e) of the act rather than under 505(j)(5) of the act. This result is procedurally fair because of the different types of issues to be resolved under the two sections of the act. When the agency proposes to withdraw an ANDA under section 505(e) of the act, rather than section 505(j)(5) of the act, **the basis for withdrawal will directly concern aspects of safety and effectiveness, labeling, or manufacturing** that are specific to the ANDA holder's product; the basis for such a withdrawal will not be the safety and effectiveness of the underlying drug substance. **In a 505(e) proceeding that concerns only a specific ANDA and not the underlying drug substance, therefore, the ANDA holder will be in the best position to present relevant evidence and to represent its interests**. In many instances, an ANDA holder alone will possess the information essential to resolving factual issues necessary for the agency to make an informed judgment about whether or not approval of the application should be withdrawn or suspended for grounds specified under section 505(e) of the act.

1989 Proposed Rule at 28904, § N (emphasis added). This portion of the 1989 Proposed Rule references 21 U.S.C. §505(e), which provides various grounds under which the Secretary of the FDA can withdraw an approval of "any drug under [§505]," which would include ANDA approved drugs under §505(j). 21 U.S.C.

§505(e)-(j) (2008). One of these grounds specifically applicable to withdrawal of §505(j) generic ANDA approvals is if "on the basis of new information before him . . . the labeling of such drug . . . is false or misleading." Id. at §505(e). All this taken together suggests that a generic drug manufacturer could in fact unilaterally change its label warnings after initial ANDA approval, subject to the FDA's approval of the change and after due process proceedings on the issue of withdrawal. Therefore, not only does the 1989 Proposed Rule initially beg the question of whether generic manufacturers can make unilateral changes after ANDA approval, it actually *answers* the question by indicating that generic manufacturers can do so, subject to due process approval or withdrawal by the FDA. As a result, the 1989 Proposed Rule actually undermines Actavis's argument on preemption by indicating that generic manufacturers can make unilateral post-ANDA approval labeling changes.

Finally, this excerpt from §N of the 1989 Proposed Rule sheds light on the meaning of 21 C.F.R. §314.97 (discussed in further detail below in section C(3)). Section 314.97 provides that a generic manufacturer "shall comply with the requirements of [21 C.F.R.] §314.70," which outlines the CBE procedures that include the requirements and process for making unilateral post-approval label changes. See 21 C.F.R. §§314.70(c)(6).[2] Section 314.97 was first proposed in

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[2] 21 C.F.R. §314.70(c)(6) provides in pertinent part that the holder of an NDA approval may make labeling changes "[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction" when there is evidence of a causal association sufficient to meet the standard for label inclusion under 21 C.F.R. §201.57(c). 21 C.F.R. §314.70(c)(6)(iii)(A)(2008). The current

the 1989 Proposed Rule; additionally, in the FDA report regarding the final rulemaking process for 21 C.F.R. §314, the FDA notes that they "received no comments on [§314.97] and . . . finalized it without change." Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17950, 17965 (Apr. 28, 1992). Thus throughout the entire life of the regulations governing generic drug labeling changes, §314.97 has mandated, without any opposition or comment, that generic manufacturers "shall comply" with the CBE labeling change provisions of §314.70(c)(6). As a result, generic manufacturers should be able to unilaterally change their labels after initial ANDA approval, albeit subject to FDA oversight and approval under §314.70(c)(6).

Under the above analysis, the appropriate level of deference that this Court should give the 1989 Proposed Rule is essentially irrelevant, because the 1989 Proposed Rule does not shed any pertinent light on the issue of whether the FDCA preempts Demahy's failure-to-warn claims under the LPLA. Furthermore, to the extent that the 1989 Proposed Rule is relevant

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language of this provision went into effect on September 22, 2008. The reference to the §201.57(c) evidentiary standard requires that warnings be based on "clinical data" or possibly "serious animal toxicity." 21 C.F.R. §201.57(c). Thus, the reference to §201.57(c) in §314.70(c)(6)(iii)(A) ensures that any added warnings will be sufficiently substantiated to merit inclusion on the label.

The prior version of §314.70(c)(6)(iii)(A), which would have been in effect during the period relevant to this case, provided essentially the same CBE procedure for labeling changes, but without reference to "evidence of a causal association" under §201.57(c). Regardless, the differences between the current and former versions of §314.70(c)(6)(iii)(A) are irrelevant to this analysis. See 21 C.F.R. §314.70(c)(6)(iii)(A) (2007).

at all to the issue of preemption, it actually contemplates unilateral labeling changes by generic manufacturers, and thus goes against a finding of preemption as argued by Actavis.

2) Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17950 (Apr. 28, 1992) (hereinafter "1992 Final Rule")

The next pieces of evidence cited by Actavis in support of its preemption argument are FDA comments on the final rule that enacted the federal regulations promulgated under the Hatch-Waxman amendments and which govern the ANDA application process. See 1992 Final Rule, at 17950 ("These regulations implement title I of the [Hatch-Waxman Amendments]. This final rule covers subjects such as ANDA content and format, approval and nonapproval of an application, and suitability petitions.").

Again, as with Actavis's reference to the 1989 Proposed Rule, the 1992 Final Rule specifically deals only with labeling requirements for generic manufacturers who are in the *initial ANDA application process*, and does not address post-approval labeling changes. See, e.g., 1992 Final Rule, at 17951-52. Nonetheless, Actavis cites the 1992 Final Rule for the proposition that generic labels must always be the same as name brand labels throughout the life of the generic drug. However, the section of the 1992 Final Rule that Actavis cites is the FDA's response to a public comment on 21 C.F.R. §314.1, which lays out the scope of §314, suggesting that the "FDA accept ANDA's with warnings or precautions in addition to those" on the name brand pioneer drug's label. Id. at 17953. The FDA disagreed with the

comment and stated that "the applicant's proposed labeling" for a generic ANDA must be the "same as" that of the listed name brand drug. Id. Thus, as with the 1989 Proposed Rule, the comment relates only to "applicants," not manufacturers who have already received ANDA approval, and uses the "same as" language, which is crucially different from the "consistent with" language of §314.150(b)(1). In fact, the 1992 Final Rule expressly distinguishes between ANDA "**applicants**," the manufacturers seeking ANDA approval, and ANDA "**holders**," those who have received approval. See, e.g., 1992 Final Rule at 17951 ("The final rule is substantially similar to the proposal, although FDA has made some minor changes, such as requiring **applicants** to include a table of contents in the review copies of an ANDA . . . and other minor changes regarding periodic reports from ANDA **holders**.") (emphasis added).

Further, Actavis specifically cites Comment 20 of the 1992 Final Rule, which includes the FDA's response to a public comment suggesting that generic manufacturers be allowed to submit a suitability petition[3] for an ANDA "for a product whose labeling differs from the [name brand] drug by being 'more clear or offer[ing] better directions regarding how the drug should be taken." Id. at 17957, Cmt. 20. The FDA first noted that "[l]abeling differences . . . are not proper subjects for a suitability petition," then went on to "remind[] applicants that the labeling for an ANDA

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[3] A suitability petition is the mechanism by which a manufacturer may seek approval for "drugs that have a different active ingredient, route of administration, dosage form, or strength." 1992 Final Rule, at 17957.

product must be the same as the labeling for the [name brand] product." Id. The comment also notes that an ANDA applicant who believes that the labeling for a proposed drug product should differ from that of the name brand drug should contact the FDA for a determination of whether both the generic and name brand labels should be changed. Id. Again, this section refers only to ANDA "applicants," and not to generic manufacturers who have already obtained ANDA approval.

The 1992 Final Rule does include the FDA's first suggestion that a generic manufacturer cannot make post-approval label changes without prior FDA approval. In response to a public comment suggesting that the FDA allow ANDA applicants to deviate from the name brand label to add safety-related information, the FDA suggested that "[a]fter approval of an ANDA, if an ANDA holder believes that new safety information should be added, it **should provide** adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised." Id. at 17961, cmt. 40 (emphasis added). While this suggestion supports Actavis's position that generic manufacturers cannot change their labels without prior FDA approval, the comment cannot be taken at face value. First, it should be noted that the comment is in response to a suggestion that *applicants* be allowed to deviate from the name brand label. Thus, to the extent that the FDA's response suggests that ANDA *holders* must receive FDA approval before making label changes, the response is outside the public comment's scope. Second, this non-responsive comment by the FDA flies in the face of 21 C.F.R. §314.97, which as noted above mandates that generic manufacturers shall comply

with the provisions of 21 C.F.R. §314.70, the regulation that establishes the CBE procedures. Finally, Comment 40 does not expressly preclude generic manufacturers from making unilateral label changes; it merely suggests that they "should provide" relevant information to the FDA. This permissive language in a non-responsive comment does not constitute a definitive statement by the FDA that generic manufacturers cannot unilaterally update their labels. Thus not only is this non-responsive, and merely permissive, comment extraneous, it is also inconsistent with §§314.97 and 314.70. As a result, Comment 40 is either irrelevant or merely entitled to Skidmore deference, and does not have the power to persuade in support of Actavis's preemption position.

Finally, as it did in the 1989 Proposed Rule, the FDA suggests in the 1992 Final Rule that generic manufacturers *can unilaterally change their labels* without prior FDA approval. In response to a comment suggesting that NDA and ANDA holders should submit the same post-marketing reports on their products, the FDA stated:

> After careful consideration, FDA has revised § 314.98 [the post-marketing reporting provision] to require ANDA applicants to submit a periodic report of adverse drug experiences even if the ANDA applicant has not received any adverse drug experience reports **or initiated any labeling changes**. As revised, the requirement is identical to that imposed on NDA holders. **Periodic reports by ANDA holders will help FDA determine whether ANDA products have appropriate labeling**

> and ensure that no adverse drug experiences go unreported.

1992 Final Rule, 17965, cmt. 53. This comment, in the context of post-marketing reporting requirements, *clearly* contemplates that a generic manufacturer with ANDA approval may initiate labeling changes. Furthermore, the comment anticipates such unilateral labeling changes by ANDA holders because it notes that post-marketing reporting requirements "will help FDA determine whether ANDA products have appropriate labeling," which suggests that labels may have been changed by ANDA holders after initial approval. Therefore, as in the 1989 Proposed Rule, the FDA expressly contemplates unilateral label changes by generic manufacturers with ANDA approvals. As such, the 1992 Final Rule does not support Actavis's preemption position.

Again, as with the 1989 Proposed Rule, the level of deference this Court should give the 1992 Final Rule is irrelevant since the 1992 Final Rule does not speak directly to the issue of preemption. The only suggestion of preemption in the 1992 Final Rule is couched in permissive terms, and is then undermined by the FDA's later recognition of the possibility of unilateral label changes by generic manufacturers.

Nonetheless, the 1989 Proposed Rule and the 1992 Final Rule, to the extent that they are relevant, are entitled to the high level of Chevron deference afforded agency decisions made pursuant to notice-and-comment rulemaking. However, in contrast to Actavis's arguments, the relevant portions of the 1989 Proposed Rule and 1992 Final Rule reveal that the *FDA took no direct position* on this issue of preemption

in those notice-and-comment produced statements, and even suggested the possibility of unilateral labeling changes by generic manufacturers. In fact, only very recently (see section C(4) below) has the FDA directly addressed whether generic manufacturers can unilaterally alter their labels with respect to preemption of state law failure-to-warn claims. As such, the FDA's position on preemption of state law failure-to-warn claims against generic manufacturers has *not been consistent* over the last twenty years. Moreover, the only relevant portions of the 1989 Proposed Rule and the 1992 Final Rule that are subject to Chevron deference actually suggest that the FDA *historically confirmed* the right of generic manufacturers to unilaterally alter their labels. This conclusion is bolstered by the fact that the FDCA does not expressly preempt state law products liability claims, and the fact that such claims come under the traditional and presumptively non-preempted power of the states to protect the health and safety of their citizens.

Furthermore, to the extent the 1989 Proposed Rule and the 1992 Final Rule can be construed as FDA interpretations of their ambiguous regulations on the exact issue of preemption, they would be subject to Auer deference. However, because the rules are inconsistent with other FDA statements and regulations, they are not entitled to Auer deference. As such, they are entitled to Skidmore deference only, and they do not have the power to persuade under that standard.

3) **21 C.F.R. §314.150**

The third piece of evidence allegedly supporting Actavis's arguments regarding conflict preemption is 21 C.F.R. §314.150, which has already been discussed to some extent above. Section 314.150 establishes the grounds under which the FDA can withdraw approval of an NDA or ANDA. 21 C.F.R. §314.150 (2008). Actavis cites §314.150 for the proposition that generic drugs must always follow the labeling of the name brand drug "verbatim" even after initial approval of the generic product via the ANDA process.

However, as discussed above, §314.150 does not use the word "verbatim" or the phrase "same as" in its provisions applicable to withdrawal of an ANDA based on labeling changes. The text of §314.150 provides in pertinent part that the FDA may withdraw an ANDA if "the labeling for the drug product that is the subject of the abbreviated new drug application is **no longer consistent with** that for the listed drug referred to in the abbreviated new drug application, except for differences approved in the [ANDA]." Id. Again, as noted above, the term "no longer consistent with" does not mean "verbatim," "identical," or "same as." A generic label may be "consistent with" a name brand label even if it is not exactly the "same as" that label. Further, even if the generic label includes additional warnings that do not appear on the name brand label, these additional warnings may still be "consistent with" the general purpose of the name brand label to inform the consumer of the relevant risks of the drug. Regardless, the conspicuous use of the phrase "consistent with" as opposed to the phrase "same as" which appears in the FDA's regulatory comments, and the term "verbatim" which appears in Actavis's

pleadings, suggests that generic labels may not necessarily have to be exactly the same as name brand labels throughout the life of the generic product. Thus, §314.150 does not expressly prohibit generic manufacturers from making unilateral labeling changes under the CBE process, and therefore does not support Actavis's preemption argument.

> **4) Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed Reg 2848, 2849-2850 (proposed January 16,2008) (hereinafter "2008 Proposed Rule").**

The next evidence Actavis relies on are the FDA's comments in a recent proposed rule concerning amendments to the regulations governing supplemental applications for proposed labeling changes for approved drugs. 2008 Proposed Rule, at 2848. The 2008 Proposed Rule is intended to update and codify the FDA's allegedly "longstanding view" on when labeling changes can be made without prior FDA approval via the CBE process. The 2008 Proposed Rule includes the first and only explicit notice-and-comment produced statement by the FDA that generic drug manufacturers cannot utilize the CBE label change procedure under 21 C.F.R. §314.70(c)(6)(iii)(A):

> **FN1 CBE changes are not available for generic drugs approved under an [ANDA] under 21 U.S.C. 355(j).** To the contrary, a generic drug manufacturer is required to conform to the approved labeling for the listed

drug. See 21 CFR 314.150(b)(10); see also 57 FR 17950, 17953, and 17961.

2008 Proposed Rule, at 2849, n.1 (emphasis added).

It should first be noted that the 2008 Proposed Rule's main purpose is to propose changes to the mechanics of the §314.70 CBE procedures. As a result, the 2008 Proposed Rule has *nothing whatsoever to do with* the existence or availability of those procedures to ANDA holders. Furthermore, while the FDA does expressly indicate that the CBE procedure is not available to generic drug manufacturers with ANDA approval, this comment is relegated to a mere *footnote* in the *Supplementary Section* of a *proposed rule* that *does not mention ANDA or generic manufacturers anywhere else in the entirety of the proposed rule*. The FDA essentially took the opportunity to make a significant statement on preemption of generic drug labeling claims in the relative obscurity of a footnote in the introductory statement of a document that has nothing at all to do with rules pertaining to generic drugs or to the ANDA process. The Fifth Circuit has suggested that a footnote to a finalized regulation, even though it may have been the product of notice-and-comment rulemaking, may not be entitled to Chevron or Auer deference. See Langbecker v. Elec. Data Systems Corp., 476 F.3d 299, 311 n.22 (5th Cir. 2007). As such, a footnote in a *proposed* rule should not be afforded any significant level of deference.

Additionally, this statement in a footnote in the 2008 Proposed Rule *contradicts the FDA's own regulations*. As noted above, 21 C.F.R. §314.97 provides in full: "[an ANDA applicant] shall comply with the requirements of §§ 314.70 and 314.71 regarding the

submission of supplemental applications and other changes to an approved abbreviated application." 21 C.F.R. §314.97 (2008). Thus because §314.70(c)(6)(iii)(A) explicitly allows for unilateral labeling changes, and since §314.97 explicitly mandates that ANDA applicants and holders "shall comply" with §314.70, the FDA's statement that generic manufacturers with ANDA approval cannot utilize CBE labeling changes *directly contradicts the FDA's own regulations.*

Finally, and perhaps most importantly, even if the FDA's footnoted statement in the 2008 Proposed Rule were not extraneous and contradictory, it is entitled to no deference whatsoever under Fifth Circuit precedent. In no uncertain terms, the Fifth Circuit has held that "proposed regulations are entitled to no deference until final." In Re Appletree Markets, Inc., 19 F.3d 969, 973 (5th Cir. 1994). Therefore, not only is the statement that generic manufacturers cannot make CBE labeling changes irrelevant in its own context and contradictory to the FDA's own regulations, it is not entitled to any deference at all under Fifth Circuit law. Therefore, the 2008 Proposed Rule does nothing to support Actavis's position.

a) Cases Applying the Non-Preemption Analysis

Further, and consistent with the above analysis, the District Court for the Western District of Washington has held that generic drug manufacturers have the same ability as name brand manufacturers to unilaterally update their labels via the CBE provisions of §314.70. Laisure-Radke v. Par Pharm., Inc, 2006 WL 901657 (W.D. Wash. 2006). The Laisure-Radke court

was faced with the same issue currently before this Court, namely whether there was a conflict between Washington state law failure-to-warn claims based on generic drug labels and the FDCA. Id. at *3. The defendant generic drug manufacturer in Laisure-Radke argued that under the Hatch-Waxman Amendments to the FDCA and 21 C.F.R. §314.94, which requires ANDA applicants to submit side-by-side comparisons of the approved name brand and proposed generic labels, "a generic manufacturer simply cannot deviate its labeling from that of the [name brand] drug." Id. The court noted that generic and name brand labels must indeed be identical during the initial ANDA approval process, but found that "*once the ANDA is approved*, generic manufacturers have the same power and duty to add or strengthen their warnings, as do the manufacturers of pioneer drugs, and therefore the same liability." Id. (emphasis in original). The Laisure-Radke court relied on the Fourth Circuit's 1994 decision in Foster v. American Home Products Corp., which reviewed the issue of whether a name brand manufacturer can be held liable for negligent misrepresentation caused by another company's generic product. Id. (citing Foster, 29 F.3d 165 (4th Cir. 1994). The Foster court held that under 21 C.F.R. §§314.70 and 314.97, generic manufacturers have the same ability to alter a generic drug's labeling to strengthen or add warnings as name brand manufacturers. Id. at *4 (citing Foster, 29 F.3d at 169). Although the Foster court addressed a different legal issue, the Laisure-Radke court found its reasoning persuasive. As such, the Laisure-Radke court held that under §314.70, which expressly applies to generic drug manufacturers under §314.97, "once a generic drug manufacturer holds an approved ANDA for a particular product, it can add or strengthen a

contraindication, warning, precaution or adverse reaction at any time without prior FDA approval." Id. at *5.

It should be noted that the Laisure-Radke decision was handed down in 2006, before the FDA's footnoted statement in the 2008 Proposed Rule that generic manufacturers cannot utilize the CBE process to make unilateral label changes. However, as discussed above, the statement in the 2008 Proposed Rule is contradictory and extraneous, and also commands no deference from a Fifth Circuit court.

Further, several cases have agreed with the Foster/Laisure-Radke analysis even after the advent of the 2008 Proposed Rule. Like the Foster case, these cases arose in the context of claims against name brand manufacturers for failure to update their own labels, which in turn rendered the labels of generic drugs inadequate. Thus, these cases essentially involved claims against name brand manufacturers for faulty labeling on generic drugs that the name brand manufacturers did not even produce. See, e.g., Swicegood v. Pliva, Inc., 543 F. Supp. 2d 1351, 1358 (N.D. Ga. 2008); Morris v. Wyeth, 2008 WL 2677048, *3 (W.D. Ky. 2008); Smith v. Wyeth, Inc., 2008 WL 2677051, *3 (W.D. Ky. 2008); Wilson v. Wyeth, Inc., 2008 WL 2677049, *3 (W.D. Ky. 2008).[4] Due to the posture of these cases, the issue of preemption was not raised by the parties, and as such the courts either

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[4] The cases from the Western District of Kentucky were apparently all related as the decisions employ virtually identical language and all deal with issues of liability for generic labeling of metoclopramide.

expressly avoided the preemption issue, or spoke on the issue in dicta only. See, e.g. Swicegood, 543 F. Supp. 2d at 1358 n.1 (noting that defendants did not argue for dismissal based on federal statutory preemption, but also noting that Georgia courts have held that state common law claims are not preempted by the FDCA). Nonetheless, all these cases rely to some degree or another on the policy arguments presented in Foster:

> We do not accept the assertion that a generic manufacturer is not responsible for negligent misrepresentations on its product labels if it did not initially formulate the warnings and representations itself. When a generic manufacturer adopts a name brand manufacturer's warnings and representations without independent investigation, it does so at the risk that such warnings and representations may be flawed. In cases involving products alleged to be defective due to inadequate warnings, the manufacturer is held to the knowledge and skill of an expert . . . . The manufacturer's status as expert means that at a minimum he must keep abreast of scientific knowledge, discoveries, and advances and is presumed to know what is imparted thereby. The same principle applies in the instant case; as an expert, a manufacturer of generic products is responsible for the accuracy of labels placed on its products. Although generic manufacturers must include the same labeling information as the equivalent name brand drug, they are also permitted to add or strengthen warnings and delete misleading statements on labels, even without prior FDA approval. 21 C.F.R.§ 314.70

> (1993). The statutory scheme governing premarketing approval for drugs simply does not evidence Congressional intent to insulate generic drug manufacturers from liability for misrepresentations made regarding their products, or to otherwise alter state products liability law. **Manufacturers of generic drugs, like all other manufacturers, are responsible for the representations they make regarding their products.**

Foster, 29 F.3d at 169-70 (internal quotations and citations omitted) (emphasis added). In the context of the above language from Foster, the Swicegood court held that "Defendant [generic manufacturer] had the ability - albeit with approval from the FDA - to add to or strengthen a contraindication, warning, precaution, or adverse reaction." 543 F. Supp. 2d at 1358 (citing 21 C.F.R. §314.70 and Colacicco v. Apotex, Inc., 432 F. Supp. 2d 514, 523 (E.D. Pa. 2006)). Also, the Morris/Smith/Wilson cases held that "FDA regulations allow the manufacturer of a generic drug "[t]o add or strengthen a contraindication, warning, precaution or adverse reaction . . . without prior FDA approval." Morris, 2008 WL 2677048 at *4; Smith, 2008 WL 2677051 at *4; Wilson, 2008 WL 2677049 at *4. While these courts did not squarely address the issue of preemption, they relied on the Foster/Laisure-Radke policy analysis, which is itself supported by the interplay between §§314.70 and 314.97. Thus these cases support the proposition that state law failure-to-warn claims are not preempted by the Hatch-Waxman Amendments or the relevant FDA statements on preemption.

Finally, the California Court of Appeal has recently held that the FDCA does not preempt state-law failure-to-warn claims. McKenney v. Purepac Pharm. Co., 83 Cal. Rptr. 3d, 810 (Cal. App. 5th Dist. Sept. 25, 2008). The McKenney case involved the same defendant[5] as in this case and the same failure-to-warn claims under California law based on the absence of a tardive dyskenesia warning on the label for generic metoclopramide. Id. at 813. Citing the 1992 Final Rule for support, the McKenney court found "no reason to distinguish between original or [name brand] drugs and their generic equivalents for federal preemption purposes." Id. at 818. Thus, the McKenney court correctly noted that the 1992 Final Rule actually takes a *non-preemption* position, and properly concluded that the FDA's conflicting statements do not support preemption.

Actavis has cited several other post-2008 Proposed Rule decisions that have found preemption of state law failure-to-warn claims for inadequate generic drug labeling based on the FDA's statement in the proposed rule. See Mensing v. Wyeth, ---- F. Supp. 2d ----, 2008 WL 2444689, * 8 (W.D. Minn. 2008); Gaeta v. Perrigo Pharmaceuticals Co., 2008 WL 2548813, *4 (N.D. Cal. 2008); Bolin v. Smithkline Beecham Corp., 2008 WL 3286973, *8 (S.D. Fla. 2008); Masterson v. Apotex Corp., 2008 WL 3262690, *4 (S.D. Fla. 2008); Valerio v. Smithkline Beecham Corp., 2008 WL 3286976, *8 (S.D. Fla. 2008). However, none of these cases address the apparent contradiction between the FDA's statement in the 2008 Proposed Rule and the clear

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[5] As noted above, Actavis was formerly Purepac Pharmaceutical Company.

mandate of §314.97 that generic manufacturers "shall comply" with the requirements of §314.70. As such, the analysis of the Foster/Laisure-Radke cases is more persuasive, since that analysis takes into account the contradiction between the footnoted language of the 2008 Proposed Rule and the binding mandate of §§314.97 and 314.70.

Additionally, none of the cases cited by Actavis distinguish between the "consistent with" language of §314.150, which is the regulation that Actavis and most other generic manufacturers have relied on for the proposition that generic labels must always be the "same as" name brand labels, and the "same as" language used in the FDA's comments on the regulation during the proposal and final rulemaking processes (in the 1989 Proposed Rule and the 1992 Final Rule).

Finally, none of these cases address the fact that the 1989 Proposed Rule and the 1992 Final Rule actually suggest a non-preemption position, as noted by the McKenney court. Accordingly, these cases are not persuasive.

b) The Mensing Decision

The case cited by Actavis that most directly supports the FDA and Actavis's preemption position is Mensing v. Wyeth, which was expressly adopted by the other 2008 cases from the Southern District of Florida that Actavis has cited. ---- F. Supp. 2d ----, 2008 WL 2444689 (W.D. Minn.); see also Bolin v. Smithkline Beecham Corp., 2008 WL 3286973, 8 (S.D. Fla. 2008). As such, a close reading and criticism of the Mensing decision will bolster the non-preemption analysis.

Mensing involved the exact same claims that Demahy has brought before this Court, namely that generic metoclopramide manufacturer Actavis negligently failed to include warnings of the risk of tardive dyskinesia on its labels in violation of state law failure-to-warn duties. 2008 WL 3286973 at *1. Specifically, the Mensing plaintiff argued that "Actavis . . . ignored scientific and medical literature establishing a higher risk of developing tardive dyskinesia, failed to request a labeling revision to the FDA, and failed to report safety information directly to the medical community." Id. In opposition, Actavis argued that plaintiff's claims were conflict preempted. Id. In response to the preemption argument, plaintiff asserted that while generic manufacturers may be required to submit identical labels to that of the name brand drug during the *initial* ANDA approval process, they nonetheless have a duty to update their labels *post-ANDA* approval to include newly discovered warnings. Id.

The Mensing court initially considered the pertinent provisions of the FDCA, the legislative history of the act, the governing regulations, and the FDA's comments on the regulations to conclude that a generic manufacturer cannot unilaterally alter its labels. Id. at *5. In support of its finding of preemption, the Mensing court initially cited the 1989 Proposed Rule in holding that "the FDA's own comments in implementing the Hatch-Waxman Act support the conclusion that a generic manufacturer is not free to unilaterally alter the labeling from that of the name brand drug." Id. However, as noted in the above discussion, the 1989 Proposed Rule was concerned only with pre-ANDA approval requirements, not post-ANDA approval duties. Also, the 1989 Proposed Rule

itself goes on to suggest that generic manufacturers *can* unilaterally change their labels post-ANDA approval, subject to FDA approval. See 1989 Proposed Rule at 28904, § N (discussed above at section C(1)).

Next, the Mensing court cited §314.150 and the portions of the 1992 Final Rule discussed in section C(2) above to support its finding of preemption. Mensing, 2008 WL 2444689 at * 5-6. Specifically, the Mensing court noted that §314.150 allows for withdrawal of an ANDA if a generic label is no longer "consistent with" the name brand label, and quoted the 1992 Final Rule comment that "[a]fter approval of an ANDA, if an ANDA holder believes that new safety information should be added, it should provide adequate supporting information to FDA" for the FDA to determine whether a label change is appropriate. Id. However, the Mensing court did not discuss the significant difference between the "consistent with" language of §314.150 and the "same as" language used throughout the FDA's 1989 Proposed Rule and 1992 Final Rule. Also, the Mensing court did not point out that the "should provide" language of the 1992 Rule is simply permissive and not mandatory, whereas the language of §314.97 is mandatory. Finally, the Mensing court ignored other statements by the FDA in the 1992 Final Rule that suggest that generic manufacturers can unilaterally alter their labels.

The Mensing court also disagreed with plaintiff's argument that the CBE mechanism provided in §314.70 allows generic drug manufacturers to make unilateral label changes. Relying on an FDA amicus brief, the Mensing court pointed out the FDA's argument that:

> Although [21 C.F.R. §314.97] contains a provision requiring [ANDA] applicants to 'comply with the requirements of §314.70 . . .' *that provision does not modify the requirement that the drug label for a generic drug must be the* ***same as*** *the label for the approved innovator drug . . . Any ambiguity in the regulatory text has been clarified by FDA, which explained at the time of the promulgation that the regulations do not authorize drug manufacturers to add new warnings to the approved labeling for the innovator drug.* ***See*** 57 Fed. Reg. at 17961, 17953, 17955.

Mensing, 2008 WL 2444689 at *7 (emphasis in original).

Although the Mensing court may have been entitled to rely on the FDA's amicus position regarding the ambiguity between §314.97 and §314.70, this Court is not required to give full deference to the FDA's statements in an amicus brief. See Belt v. EmCare, Inc., 444 F.3d 403, 416 n.35 (5th Cir. 2006) (noting that Auer deference, not Chevron deference, is appropriate for informal agency interpretations "such as . . . *amicus curiae* briefs"). Furthermore, Auer deference is only appropriate if the regulation being interpreted is actually ambiguous; otherwise, only Skidmore deference is necessary. Moore v. Hannon Food Service, Inc., 317 F.3d 489, 494-95 (5th Cir. 2003). Although the FDA claimed in Mensing that it had "clarified" any "ambiguity" in the regulations with respect to the provisions of §314.97, the provisions of that regulation are simple, concise, and patently unambiguous. Therefore, only Skidmore deference is necessary. Accordingly, because the FDA position in Mensing

cited only the 1992 Final Rule, with all its internal inconsistencies and irrelevancies, to support its position that it has clarified any ambiguities with regard to §314.97, this Court need not give that position any deference since it does not have the "power to persuade" under Skidmore. Furthermore, the FDA position cited in Mensing makes the assertion that a generic drug label must always be the "same as" the name brand label, without citing to any definitive source for that assertion. This may be due to the fact that there *is no definitive regulation* that dictates that generic drug labels must *always* be the "same as" the corresponding name brand label. As a result, the FDA's position that generic labels must always be the "same as" the name brand label is also not entitled to Auer deference because that position is inconsistent with the regulations at issue. As such, only Skidmore deference applies, and since the FDA's position cannot persuade, it should receive no deference.

Finally, the Mensing court relied on the FDA's footnote in the supplementary introduction to the 2008 Proposed Rule indicating that generic manufacturers cannot unilaterally change their labels. Mensing, 2008 WL 2444689, *8. As discussed above, Fifth Circuit courts need not give any deference to an agency's statements in proposed rules. Additionally, the FDA's footnote in the 2008 Final Rule is extraneous to the purpose of the proposed rule and is contradictory to the FDA's own regulation in §314.97. As such, the Mensing court's analysis is not persuasive in this matter.

5) Colacicco v. Apotex, Inc. – 432 F. Supp. 2d 514, 528-29 (E.D. Penn. 2006) (aff'd 521 F.3d 253 (3d Cir. 2008)

The final piece of evidence Actavis presented to this Court in support of its preemption position was the Eastern District of Pennsylvania's decision in Colacicco v. Apotex, Inc., which determined that the FDCA preempts state law failure-to-warn claims against generic drug manufacturers. It should first be noted that the Third Circuit in affirming the Colacicco district court's decision expressly left open the question of "whether actions against generic drug manufacturers are preempted on the basis of their obligations under the Hatch-Waxman Amendments [and limited its holding] to circumstances in which the FDA has publicly rejected the need for a warning that plaintiffs argue state law requires." Colacicco v. Apotex, Inc., 521 F.3d 253, 271-272 (3d Cir. 2008). There is no allegation or record evidence in the instant case regarding whether the FDA considered and rejected a neurological risk warning for generic metoclopramide. As such, the Third Circuit's decision has no relevance to the specific issue before this Court, namely whether claims against a generic manufacturer are preempted under the Hatch-Waxman Amendments in circumstances in which the FDA has *not publicly rejected* a proposed warning. Therefore, Actavis's assertion that the Third Circuit in Colacicco agreed with the "FDA's longstanding position . . . that a plaintiff's state law failure to warn claims asserted against a generic drug manufacturer are conflict-preempted as a matter of law" is patently erroneous. Def.'s Reply Memo Opp. Summ. J., 1.

Nonetheless, Actavis points this Court to the Colacicco district court's opinion on the issue of preemption of state law failure-to-warn claims against generic manufacturers. Colacicco was fundamentally different from this case in that it involved Pennsylvania state law claims against both name brand and generic manufacturers for failure to warn of the increased risk of suicide caused by certain anti-depressant medications. Colacicco v. Apotex, Inc., 432 F. Supp. 2d 514, 520 (E.D. Pa. 2006). As such, the Colacicco district court's opinion addressed FDA preemption statements with respect to claims against both name brand and generic manufacturers. After a lengthy discussion of the proper level of deference that should be given to FDA position statements on the issue of preemption, the Colacicco district court determined that it should give deference to the government's amicus briefs filed in the case as well as the FDA's 2006 Preemption Preamble.[6] Id. at 524-25.

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[6] The so-called "Preemption Preamble" is the FDA statement that initiated the FDA's broad position regarding preemption of state law failure-to-warn claims under the FDCA. See 71 Fed. Reg. 3922-01, 3933-3936, part D. Comments on Product Liability Implications of the Proposed Rule (Jan. 24, 2006). The Preemption Preamble generally and broadly states the FDA's position that it alone has authority to make the final decision regarding the safety and labeling of prescription drugs, and therefore state law products liability claims against prescription drug manufacturers should be preempted. However, because the Preemption Preamble does not deal specifically with claims against *generic* drug manufacturers, its relevance to the instant case is minimal.

Furthermore, this final preamble section to the rulemaking comments was not subject to the strictures of the rulemaking process, and in fact "*conflict[s]* with statements made in the original notice of proposed rulemaking out of which the 2006 Final Rule grew" See In Re Vioxx, 501 F. Supp.2d 776, 787 (E.D. La.

In response to the plaintiff's specific argument that the §314.70 CBE procedure allows generic drug manufacturers to unilaterally update their labels, the Colacicco district court held that "principles of deference do not allow us to question the FDA's interpretation of its own regulations - e.g. that generic drug manufacturers can not (sic) make changes without prior approval." Id. at 528. The Colacicco district court therefore relied solely on the text of §§314.70 and 314.150, as well as statements by the FDA in the 1992 Final Rule (discussed above in section C(2)) as a basis for its "deference" to the FDA's position on preemption.

Prominently absent from the Colacicco district court's analysis is any discussion of §314.97, the regulation that specifically mandates generic manufacturers to comply with the provisions of §314.70. Furthermore, as noted numerous times in this discussion, the FDA's comments in the 1992 Final Rule regarding whether generic manufacturers can unilaterally update their labels are not entitled to deference because they are inconsistent and ambiguous.

2007) (emphasis added). In fact, the initial proposed rulemaking notice actually expressly stated that "this proposed rule does not preempt State law . . . [nor] contain policies that have federalism implications or that preempt state law." Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels, 65 Fed. Reg. 81082, 81103 (Dec. 22, 2002). Accordingly, and despite Actavis's argument to the contrary, only Skidmore deference would be appropriate in the context of the Preemption Preamble. As such, to the extent it is at all relevant to this case, it does not have the power to persuade.

Therefore, because the Colacicco district court decision involved crucially different facts as well as a deference position that is inconsistent with the views of this Court's analysis, this Court does not afford the Colacicco district court's decision persuasive weight in this matter.

6) Summary

In sum, none of the evidence cited by Actavis in this case is dispositive on the issue of whether Demahy's LPLA failure-to-warn claims are preempted under the FDCA and the applicable regulations and FDA statements. The 1989 Proposed Rule and 1992 Final Rule are generally entitled to Chevron deference, but since those documents do not answer the discrete question before this court, they are irrelevant regardless of the appropriate level of deference. Further, to the extant they are relevant, the 1989 Proposed Rule and the 1992 Final Rule actually contemplate unilateral labeling changes by generic drug manufacturers. Also, to the extent that those statements interpret ambiguous FDA regulations as precluding unilateral label changes by generic manufacturers, they would merit Auer deference. However, because they are inconsistent with the unambiguous language of §314.97 and §314.70 and are thus unreasonable, they are only entitled to Skidmore deference and do not have the power to persuade.

Additionally, the FDA's interpretations of §314.150 are entitled only to Skidmore deference since those interpretations are not consistent with other regulations, namely §314.70 and §314.97, nor are they consistent with other FDA statements on the issue of labeling changes. Thus, these statements should not

receive Auer deference, as they are inconsistent with valid regulations, and do not have the power to persuade as a matter of Skidmore deference because they are inconsistent and contradictory.

Furthermore, the 2008 Proposed Rule is not entitled to any deference in this Court, and the cases relying on that rule are inapposite and unpersuasive.

Finally, the Colacicco case involved crucially different facts in that the proposed warning at issue in that case had been *expressly rejected by the FDA*.

As such, this Court finds that Demahy's failure-to-warn claims under the LPLA are not preempted as a matter of conflict preemption under the FDCA, applicable regulations, and relevant FDA position statements. Accordingly,

IT IS ORDERED that Actavis's Rule 12(b)(6) Motion to Dismiss Demahy's LPLA failure-to-warn claims under a theory of federal conflict preemption is hereby **DENIED**.

However, to the extent that Demahy's claim constitutes a fraud-on-the-FDA claim against Actavis, that claim is preempted under the Supreme Court's ruling in Buckman Co. v. Plaintiff's Legal Committee, 531 U.S. 341, 348 (2001). Accordingly,

IT IS FURTHER ORDERED that Actavis's Rule 12(b)(6) Motion to Dismiss Demahy's claims, to the extant that they allege fraud-on-the-FDA claims under Louisiana law, is hereby **GRANTED.**

New Orleans, Louisiana this 27th day of October, 2008.

/s/ Carl J. Barbier
CARL J. BARBIER
UNITED STATES DISTRICT JUDGE

IN THE UNITED STATES COURT OF APPEALS FOR THE FIFTH CIRCUIT

No. 08-31204

[Filed January 8, 2010]

JULIE DEMAHY

Plaintiff-Appellee

v.

ACTAVIS, INC., Individually and as Successor in Interest of Purepac Pharmaceutical Company

Defendant-Appellant

Appeal from the United States District Court for the Eastern District of Louisiana

Before KING, HIGGINBOTHAM, and CLEMENT, Circuit Judges.

PATRICK E. HIGGINBOTHAM, Circuit Judge:

This case presents one issue on appeal: whether the federal regulatory regime governing pharmaceuticals preempts state-law failure-to-warn claims against manufacturers of generic drugs. The Supreme Court held, in *Wyeth v. Levine*, that such claims are not

preempted against name brand drug manufacturers.[1] While not directing our result, it shadows our conclusion that the federal regulatory regime governing generics is also without preemptive effect.

I

Julie Demahy's physician prescribed the drug Reglan to treat her gastroesophageal reflux. For the next four years, Demahy's pharmacy filled her prescription with the generic form of Reglan, metoclopramide, manufactured by Actavis.[2] Demahy alleges that its long-term ingestion caused her to develop tardive dyskinesia, a neurological movement disorder.

The Food and Drug Administration (FDA) approved Reglan in 1980, and Actavis began manufacturing generic metoclopramide thereafter. In 1985, the FDA required that Reglan's label be updated to include a warning regarding the risk of developing tardive dyskinesia. Actavis revised its labeling to comport with these changes to the Reglan label. There is no dispute that the generic drug's label was at all relevant times the same as Reglan's. In February 2009, the FDA issued a labeling revision for metoclopramide meant to warn of the risk of prolonged use, defined as use for more than 12 weeks.[3]

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[1] 129 S. Ct. 1187 (2009).

[2] Formerly Purepac Pharmaceutical Company.

[3] Letter from Joyce Korvick, Deputy Dir. for Safety, Div. of Gastroenterology Products, Center for Drug Evaluation and Research, FDA, to NDA holders for Reglan, at 3 (Feb. 26, 2009)

Demahy asserts claims of personal injury under the Louisiana Products Liability Act for, *inter alia*, failure to warn of the risks of neurological disorder after long-term use of metoclopramide.[4] Specifically, Demahy argues that Actavis ignored scientific and medical literature establishing a higher risk of developing tardive dyskinesia, failed to request a labeling revision from the FDA, failed to change the label itself even though no prior FDA approval was required, and failed to report safety information directly to the medical community.

Actavis moved to dismiss Demahy's claims, arguing that they rested on duties imposed by state law that could not be met under federal law—that they were conflict preempted. The district court denied the motion as to the failure-to-warn claims.[5] Since then, one sister circuit—the Eighth[6]—has considered the issue, which has split a rapidly growing number of

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("Prolonged treatment (greater than 12 weeks) with metoclopramide should be avoided in all but rare cases where therapeutic benefit is thought to outweigh the risks to the patient of developing tardive dyskinesia.").

[4] LA. REV. STAT. 9:2800.51 *et seq.* The district court dismissed without prejudice Demahy's initial claims against defendants Wyeth, Inc., the manufacturer of brand-name metoclopramide, and Schwarz, Inc., another generic manufacturer, after Demahy's pharmacy records indicated she had taken only Actavis-manufactured metoclopramide.

[5] Actavis's 12(b)(6) motion also argued—successfully—that Demahy's fraud-on-the-FDA claims were conflict preempted. The only claims at issue on appeal are those alleging a failure to warn.

[6] *Mensing v. Wyeth*, 588 F.3d 603 (8th Cir. 2009).

district courts;[7] it held that state tort law is not

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[7] District court cases finding state law preempted include *Gaeta v. Perrigo Pharm. Co.*, ___ F. Supp. 2d ____, 2009 WL 4250690 (N.D. Cal. Nov. 24, 2009) (order denying plaintiffs' motion for reconsideration); *Smith v. Wyeth*, 2009 WL 425032 (W.D. Ky. Feb. 20, 2009) (unpublished), *Morris v. Wyeth*, 642 F. Supp. 2d 677 (W.D. Ky. 2009), *Wilson v. Pliva*, 640 F. Supp. 2d 879 (W.D. Ky. 2009), *Masterson v. Apotex Corp.*, 2008 WL 3262690 (S.D. Fla. Aug. 7, 2008) (unpublished), and *Mensing v. Wyeth*, 562 F. Supp. 2d 1056 (D. Minn. 2008), preemption holding overruled by *Mensing v. Wyeth*, 588 F.3d 603 (8th Cir. 2009). Those finding no preemption include *Munroe v. Barr Labs., Inc.*, ___ F. Supp. ____, 2009 WL 4047949 (N.D. Fla. Oct. 15, 2009); *Bartlett v. Mutual Pharm. Co.*, ___ F. Supp. ____, 2009 WL 3126305 (D.N.H. September 30, 2009), *Stacel v. Teva Pharm.*, 620 F. Supp. 2d 899 (N.D. Ill. 2009), *Kellogg v. Wyeth*, 612 F. Supp. 2d 421 (D. Vt. 2008), *Tucker v. SmithKline Beecham Corp.*, 596 F. Supp. 2d 1225 (S.D. Ind. 2008) (reversing its earlier ruling dismissing the case on preemption grounds), *Barnhill v. Teva Pharm.*, 2007 U.S. Dist. LEXIS 44718 (S.D. Ala. 2007) (unpublished), and *Laisure-Radke v. Par Pharm., Inc.*, 2006 WL 901657 (W.D. Wash. March 29, 2006) (unpublished). *See also McKenney v. Purepac Pharm. Co.*, 167 Cal. App. 4th 72 (Cal. App. 2008) (finding no preemption) *Barhoum v. Barr Pharm., Inc.* (N.J. Super., L. Div., Aug. 1 2008) (unpublished) (same); *Kelly v. Wyeth, Inc.*, 22 Mass. L. Rep. 384 (Sup. Ct. 2007) (same).

Actavis also urges this court to consider *Colacicco v. Apotex, Inc.*, 521 F.3d 253 (3d Cir. 2008) as persuasive. *Colacicco*, a pre-*Levine* case, found FDA failure-to-warn preemption as to both generic and name brand manufacturers, relying entirely on the rationale rejected by *Levine*. The Supreme Court later vacated and remanded for further consideration in light of *Levine*. *Colacicco v. Apotex, Inc.*, 129 S. Ct. 1578 (2009). Unlike the instant case, the heightened labeling requirement allegedly required by state law in *Colacicco* had been *expressly considered and rejected* by the FDA. 521 F.3d at 269. Given the vacatur of the Third Circuit's opinion, as well as the case's factual dissimilarity, we find it neither applicable nor persuasive here.

preempted.[8] Appeals involving materially identical preemption claims are now pending before the Sixth Circuit.[9] Our review here is de novo.[10]

II

All prescription drugs marketed in this country must first receive FDA approval. Manufacturers of new drugs must submit a new drug application (NDA) to the FDA that demonstrates the drug's effectiveness and safety for its intended use.[11] The 1962 Food, Drug and Cosmetics Act (FDCA) established this avenue for pioneer drugs, with the core objective of ensuring that drugs are both safe and effective;[12] the FDA has codified the NDA regulations at 21 C.F.R. Part 314. New drug approval requires, among other deliverables, the results of successful clinical trials[13] and labeling

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[8] *Mensing*, 588 F.3d at 612.

[9] *Smith v. Wyeth*, No. 09-5460 (6th Cir.); *Wilson v. Pliva*, 09-5466 (6th Cir.); *Morris v. Wyeth*, 09-5509 (6th Cir.).

[10] *See Carden v. General Motors Corp.*, 509 F.3d 227, 230 (5th Cir. 2007) (citing *Frank v. Delta Airlines, Inc.*, 314 F.3d 195, 197 (5th Cir. 2002)).

[11] *See* Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17950 (1992) (outlining the NDA process).

[12] *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 142 (2000).

[13] 21 U.S.C. § 355(b)(1) (requiring certain specified data including "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use" and "a full list of the articles used as components of such drug"). Approval is assured absent specified grounds for

that accurately portrays the benefits and risks of the drug, as indicated by those trials and other data.[14] "Before approving an NDA . . . [the] FDA undertakes a detailed review of the proposed labeling, allowing only information for which there is a scientific basis to be included in the FDA-approved labeling."[15] The FDA will reject the proposed labeling if "based on a fair evaluation of all material facts, such labeling is false or misleading in any particular."[16]

Contrast this with the simpler, less demanding approval process required of generic drugs. In 1984, Congress passed the Hatch-Waxman Amendments to the FDCA, which altered the federal regulatory regime governing generics. Thanks to these Amendments, once a pioneer drug loses patent protection, a drug company may seek permission to market a generic version through a significantly simplified process, known as the abbreviated new drug application procedure, or ANDA.[17] ANDA drugs must be the "same as" a name brand drug that has already been approved by the FDA as to active ingredients, route of

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denial, such as a failure to "include adequate tests . . . to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof" or "results of such tests [that] show [the] drug is unsafe for use under such conditions." 21 U.S.C. § 355(d).

[14] *See* 21 U.S.C. § 355; 21 C.F.R. § 314.105(b).

[15] 73 Fed. Reg. 49603, 49604 (2008).

[16] *See* 21 U.S.C. § 355; 21 C.F.R. § 314.105(b).

[17] *See* 57 Fed. Reg. 17950, 17951 (describing the Hatch-Waxman Amendments).

administration, dosage form, strength, and conditions of use recommended in the labeling.[18] Under Hatch-Waxman, generic drug manufacturers need not repeat the clinical work of their name brand counterparts, but instead must only establish the generic drug's bioequivalence with the name brand drug.[19] By avoiding "unnecessary," "wasteful," and "unethical" duplication of previously-performed human clinical trials,[20] Congress meant "to provide a careful balance between promoting competition among pioneer . . . and generic drugs, and encouraging research and innovation."[21] In turn, this increased competition, coupled with the elimination of "retesting" of a drug that has already been determined to be safe and effective,[22] would result in significant cost savings to the American public.[23] Indeed, the Congressional Budget Office estimated that generic drugs save American consumers between $8 billion and $10 billion

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[18] 21 U.S.C. § 355(j)(2)(A)(iii).

[19] 21 U.S.C. § 355(j)(2)(A)(iv).

[20] H.R. Rep. No. 98-857, pt. 1, at 16, 1984 U.S.C.C.A.N. at 2649.

[21] Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28872, 28874 (proposed July 10, 1989). *See also Mead Johnson Pharm. Group v. Bowen*, 838 F.2d 1332, 1333 (D.C. Cir. 1988) (Hatch-Waxman's purpose "was to increase competition in the drug industry by facilitating the approval of generic copies of drugs.").

[22] H.R. Rep. No. 98-857, pt. 1, at 16, 17.

[23] *Mead Johnson*, 838 F.2d at 1333.

each year.[24] Generic drugs now account for seven out of ten prescriptions filled in the United States.[25]

In their application, generic manufacturers must also show "that the labeling proposed for the new drug is the *same as* the labeling approved for the listed drug."[26] Applying to market a generic drug, then, requires "[a] statement that the applicant's proposed labeling is the same as the labeling of the reference listed drug except for" enumerated differences irrelevant here; without such a statement, the FDA will deny the application.[27]

III

The Supreme Court ruled in *Levine* that the federal regulatory regime governing pharmaceuticals does not preempt a state-law failure-to-warn claim against the manufacturer of a name brand drug. Actavis urges that generic drugs are different because the manufacturer of a name brand drug may change its label unilaterally—through the "changes being

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[24] *See* How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry, A Congressional Budget Office Study, July 1998.

[25] Susan Okie, Multinational Medicines—Ensuring Drug Quality in an Era of Global Manufacturing, 361 NEW ENG. J. MED. 737, 738 (2009).

[26] 21 U.S.C. § 355(j)(2)(A)(v) (emphasis added), 21 U.S.C. § 355(j)(4)(G).

[27] Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17950, 17985–86 (Apr. 28, 1992) (later codified at 21 C.F.R. §§ 314.94(a)(8)(iii)–(iv) (1993)).

effected" (CBE) process—while seeking the FDA's approval of the change. According to Actavis, a generic manufacturer, in contrast, must produce the same drug and use the same label as the name brand drug manufacturer.

The *Levine* Court did rely in part on the availability of the CBE process to reject the claim—advanced by a name brand manufacturer—that it was "impossible . . . to comply with both the state-law duties underlying those claims and its federal labeling duties."[28] The Court explained that once the risk to consumers has become "apparent," triggering a state-law duty to warn of it, "the CBE regulation permit[s] [the manufacturer] to provide such a warning before receiving the FDA's approval."[29] Though "the FDA retains authority to reject labeling changes made pursuant to the CBE regulation," the Court declined to "conclude that it was impossible for [the manufacturer] to comply with both federal and state requirements" without "clear evidence that the FDA would not have approved a change" to implement the warning.[30]

Justice Breyer wrote separately "to emphasize the Court's statement that 'we have no occasion in this case to consider the pre-emptive effect of a specific agency regulation bearing the force of law'"[31] and to

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[28] *Levine*, 129 S. Ct. at 1196.

[29] *Id.* at 1198.

[30] *Id.*

[31] *Levine*, 129 S. Ct. at 1204 (Breyer, J., concurring) (quoting *id.* at 1203).

accent the FDA's ability to "determine whether and when state tort law acts as a help or a hindrance to achieving the safe drug-related medical care that Congress sought" through "lawful specific regulations describing, for example, when labeling requirements serve as a ceiling as well as a floor."[32] Because no such regulation was at issue in *Levine*, Breyer agreed with the majority that state law was not preempted.[33]

Actavis rightly points out that *Levine* is not the case before us. It does, however, carry important implications for Actavis's situation as well.

IV

Here, as in every preemption case, "[t]he purpose of Congress is the ultimate touchstone."[34] Congressional intent to preempt state law can either be expressed in statutory language or implied in the aim and structure of federal law.[35] Implied preemption comes in two forms: field and conflict preemption. Field preemption is inferred where federal law is so pervasive that it leaves no room for state supplementation.[36] When Congress has not completely displaced the possibility

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[32] *Id.*

[33] *Id.*

[34] *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996) (plurality) (internal quotation marks omitted).

[35] *Hillsborough County, Fla. v. Automated Med. Labs., Inc.*, 471 U.S. 707, 712–13 (1985).

[36] *Id.*

of state regulation, preemption may nonetheless occur when state law "actually conflicts" with federal law.[37] This conflict might be with a federal statute or an "agency regulation with the force of law."[38] Actavis asserts that Demahy's claims are conflict preempted: that it is impossible to comply with both federal and state law,[39] or, alternatively that state law poses an unacceptable "obstacle to the accomplishment and execution of the full purposes and objectives of Congress."[40] More specifically, Actavis contends that it is impossible to comply with both the federal regulatory regime governing generic drugs and the putative state-imposed duty to heighten warning labels, or that Louisiana law obstructs the goals of the FDCA, as amended by the Hatch-Waxman Amendments and implemented by FDA regulation.

Such a conclusion is not to be found lightly. As *Levine* reminded, "[i]n all pre-emption cases, and particularly in those in which Congress has legislated . . . in a field which the States have traditionally occupied," a court must begin this inquiry into

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[37] *English v. Gen. Elec. Co.*, 496 U.S. 72, 79 (1990).

[38] *Levine*, 129 S. Ct. at 1200.

[39] *Crosby v. Nat'l Foreign Trade Council*, 530 U.S. 363, 372–73 (2000) (emphasis added). Instances where it is impossible to comply with both federal and state law are very rare. *Fla. Lime & Avocado Growers v. Paul*, 373 U.S. 132, 143 (1963).

[40] *Crosby*, 530 U.S. at 372–73; *see also Levine*, 129 S. Ct. at 1193–94. *But see id.* at 1204–06 (Thomas, J., concurring in the judgment) (questioning "far-reaching implied pre-emption doctrines" and explaining Thomas's increasing skepticism of the Court's "purposes and objectives pre-emption jurisprudence").

congressional intent "with the assumption that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress."[41] "We rely on the presumption because respect for the States as 'independent sovereigns in our federal system' leads us to assume that 'Congress does not cavalierly pre-empt [state law].'"[42] Though there is ongoing disagreement among Supreme Court jurists as to if, when, and how this presumption applies—particularly in implied conflict preemption cases—five members of the *Levine* Court held that it applies to conflict preemption cases at least where, as here, the question is whether federal regulation of prescription drugs preempts state-law failure-to-warn claims.[43]

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[41] *Levine*, 129 S. Ct. at 1194–95 (quoting *Lohr*, 518 U.S. at 485) (internal citations and quotation marks omitted); *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218, 230 (1947).

[42] *Levine*, 129 S. Ct. at 1195 n.3 (quoting *Lohr*, 518 U.S. at 485).

[43] *Levine*, 129 S. Ct. at 1195–96 & n.3 ("[T]he dissent argues that the presumption against pre-emption should not apply to claims of implied conflict pre-emption at all . . . but this Court has long held to the contrary."). *But see id.*, 129 S. Ct. at 1229 n.14 (Alito, J., dissenting) ("[I]t is not true that this Court has long applied a presumption against pre-emption in conflict pre-emption cases.") (internal quotation marks omitted); *see also Wells Fargo Bank of Texas, N.A. v. James*, 321 F.3d 488, 491 (5th Cir. 2003). Though Justice Thomas joined in the *Levine* majority's judgment, he declined to say whether a presumption against preemption should apply. *Levine*, 129 S. Ct. at 1208, n.2 (Thomas, J., concurring) ("Because it is evident from the text of the relevant federal statutes and regulations themselves that the state-law judgment below is not pre-empted, it is not necessary to decide whether, or to what extent, the presumption should apply in a case such as this one, where Congress has not enacted an express-pre-emption

In this case, the bar to a finding of preemption is set even higher because federal law provides no remedy for an injured consumer. Preemption of state failure-to-warn claims would foreclose a remedy that was traditionally available and for which federal law provides no substitute. Courts have been particularly reluctant to find preemption in such cases without an unambiguous signal of congressional intent.[44] This is especially true in cases that involve health and safety concerns, because "[s]tates traditionally have had greater latitude under their police powers to legislate as to the protection of the lives, limbs, health, comfort,

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clause."). In its initial brief (submitted prior to the Supreme Court's decision in *Levine*) Actavis argues that this "presumption against preemption" does not apply to conflict preemption cases. Similarly, it appears that each district court to have found failure-to-warn suits conflict-preempted has not applied the presumption against preemption. *See, e.g.*, *Mensing*, 562 F. Supp. 2d at 1061.

[44] *Lohr*, 518 U.S. at 487 ("It is, to say the least, 'difficult to believe that Congress would, without comment, remove all means of judicial recourse for those injured by illegal conduct.'") (quoting *Silkwood v. Kerr-McGee Corp.*, 464 U.S. 238, 251 (1984)); *Bates v. Dow Agrosciences LLC*, 544 U.S. 431, 449 (2005) ("If Congress had intended to deprive injured parties of a long available form of compensation, it surely would have expressed that intent more clearly."). *See also Silkwood*, 464 U.S. at 263–64 ("Because the Federal Government does not regulate the compensation of victims, and because it is inconceivable that Congress intended to leave victims with no remedy at all, the pre-emption analysis . . . comfortably accommodates—indeed it compels—the conclusion that compensatory damages are not pre-empted . . . .") (Blackmun, J., dissenting).

and quiet of all persons."[45] Moreover, Congress has already expressly preempted state failure-to-warn claims for some products governed by the FDCA—medical devices[46]—and its choice not do so for other FDA-regulated products militates further against a finding of preemption here.[47] In *Levine*, the Court found Congress's enactment of an express preemption for medical devices telling, particularly given the historic coexistence of state tort remedies and federal regulation of prescription drugs.[48] As the Supreme Court has repeatedly instructed, "[t]he case for federal pre-emption is particularly weak where Congress has indicated its awareness of the operation of state law in a field of federal interest, and has nonetheless decided to 'stand by both concepts and to tolerate whatever tension there [is] between them.'"[49]

V

Against this backdrop, Actavis first argues "that it would have been impossible for [it] to comply with the state-law duty to modify [its product's] labeling

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[45] *Lohr*, 518 U.S. at 485. *Cf. Altria Group, Inc. v. Good*, 555 U.S. ____, 129 S. Ct. 538, 543 (2008).

[46] *Riegel v. Medtronic, Inc.*, 128 S. Ct. 999, 1009 (2008). In 1997, Congress preempted certain state requirements concerning over-the-counter medications but expressly preserved product liability actions. *See* 21 U.S.C. §§ 379r(e), 379s(d).

[47] *Levine*, 129 S. Ct. at 1200.

[48] *Id.*

[49] *BonitoBoats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 166–67 (1989) (quoting *Silkwood*, 464 U.S. at 256 (1984)).

without violating federal law,"[50] i.e., that "'compliance with both federal and state [law] is a physical impossibility.'"[51] Requiring that the conflict be one of "physical impossibility" readily suggests that this is a "demanding defense."[52] Here, Actavis urges that federal law requires that it maintain at all times a label that is the "same as" the name brand's, thus preventing simultaneous compliance with a state law requiring additional warnings.

There is no dispute here that Hatch-Waxman proscribes the *approval of an application* to produce a generic drug with labeling that is not the "same as" that of the listed drug. Demahy acknowledges that a generic's label must initially conform to a listed drug's and she does not allege that Actavis is liable under state law for failure to warn adequately of the risks of tardive dyskinesia at the time of approval. Rather, she seeks to hold Actavis liable for failing to take steps to *change* the label *after approval* in order to provide adequate warning once additional risks emerged. And, while Congress plainly intended for a generic drug manufacturer to submit labeling identical to—or, the "same as"—the brand name drug when seeking ANDA approval, the statutory scheme "is silent as to the

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[50] *Levine*, 129 S.Ct. at 1199.

[51] *Fid. Fed. Sav. & Loan Ass'n v. de la Cuesta*, 458 U.S. 141, 153 (1982) (quoting *Fla. Lime & Avocado Growers, Inc. v. Paul*, 373 U.S. 132, 142–43 (1963)). *See also Barnett Bank of Marion County, N.A. v. Nelson*, 517 U.S. 25, 31 (1996) (explaining that impossibility conflict would exist "if the federal law said, 'you must sell insurance,' while the state law said, 'you may not'").

[52] *Levine*, 129 S. Ct. at 1193.

manufacturer's obligations after the ANDA is granted."[53]

Of course, this statutory silence does not end our preemption inquiry, because "state laws can be pre-empted by federal regulations as well as by federal statutes."[54] The regulations on which Actavis relies, however, do not purport to bar generic labeling modifications following initial approval. Instead, they require only that a generic's label initially conform to the listed drug's; if the label does not, these regulations provide that an ANDA application will be denied. They do not address post-approval modifications at all.[55]

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[53] *See Bartlett*, ___ F. Supp. 2d ___, 2009 WL 3126305, at *12 (quoting *Stacel*, 620 F. Supp. 2d at 907); *see also* 21 U.S.C. § 355(j)(2)(A)(v); 21 U.S.C. § 355(j)(4)(G).

[54] *Hillsborough County, Fla. v. Automated Med. Labs, Inc.*, 471 U.S. 707, 713 (1985).

[55] 21 C.F.R. § 314.94(a)(8)(i) (explaining that generic drug manufacturer must provide a copy of the currently-approved labeling for the listed name brand drug as part of its ANDA application); 21 C.F.R. § 314.94(a)(8)(iv) (requiring that, as part of its ANDA application, a generic manufacturer give a side-by-side comparison of its proposed labeling with the approved labeling for the listed drug, with all differences annotated and explained); 21 C.F.R. § 314.127(a)(7) (noting that the FDA will not approve an ANDA application if information submitted is "insufficient to show that the labeling proposed for the drug is the same as labeling approved for the listed drug"); 57 Fed. Reg. 17950, 17957 cmt. 20 ("An ANDA *applicant* who believes the labeling for a proposed drug product should differ from that approved for the reference listed drug should contact FDA to discuss whether labeling for both generic and listed drugs should be revised.") (emphasis added).

On the contrary, "through many amendments to the FDCA and to FDA regulations, it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. It is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market."[56] As for maintaining an adequate label, the regulatory framework makes plain that manufacturers —name brand and generic alike—must act to warn customers when they learn that they may be marketing an unsafe drug. For their part, generic manufacturers are subject to the requirement that their labeling "be revised . . . as soon as there is reasonable evidence of an association of a serious hazard with a drug."[57] Demahy claims that Actavis

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[56] *Levine*, 129 S. Ct. at 1197–98 (citing 21 C.F.R. § 201.80(e) and 21 C.F.R. § 314.80(b)). *See also* 21 C.F.R. § 314.80(b) (placing responsibility on the manufacturer for post-marketing surveillance).

[57] 21 C.F.R. § 201.80(e). This requirement applies to drugs, such as metoclopramide, that are not tethered to a new drug application or supplement submitted prior to July 2001. *See id.* § 201.56(b).

Congress once again revised the prescription drug regime in 2007, through the Food and Drug Administration Amendments Act. These amendments provide that, when a drug is no longer marketed by its pioneering manufacturer (the NDA holder), ANDA holders must submit a supplemental application proposing labeling changes to reflect new safety information identified by the agency, or to explain why no change is warranted. 21 U.S.C. § 355(o)(4)(B). Congress was careful to remind, however, that this obligation does not "affect the responsibility" of a generic manufacturer holding an approved ANDA "to maintain its label in accordance with existing requirements, including subpart B of part 201" and the CBE provision. *Id.* at § 355(o)(4)(I). Here, also,

failed to comply with this requirement despite reasonable evidence that long-term use of metoclopramide poses a serious hazard. Actavis responds that this requirement is on the name brand manufacturer alone, or that it is overridden as to generics, in light of the putative requirement that it conform to the name brand's label at all times.

FDA commentary supports the requirement —advanced by Demahy—that "at a minimum a generic manufacturer should alert the agency to any new safety hazard associated with its product."[88] First, in commentary accompanying the FDA's implementation of the Hatch-Waxman Amendments, the FDA stated: "After approval of an ANDA, if an ANDA holder [a generic manufacturer] believes that new safety

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the FDA intended—in apparent contradiction to the plain text of 21 C.F.R. § 201.80—to "affirm that a CBE supplement is appropriate to amend the labeling for an approved product only to reflect newly acquired information and to make it clear that a CBE supplement may be used to add or strengthen a contraindication, warning, precaution, or adverse reaction only if there is sufficient evidence of a causal association with the drug . . . ." 73 Fed. Reg. at 49604.

Though in this case the pioneering manufacturer (Wyeth) still markets the listed drug, this provision is instructive nevertheless. If, as Actavis contends, neither this provision nor the CBE process impose any "responsibility" on a generic manufacturer "to maintain its label," we are then left wondering why Congress would have deemed it necessary to clarify that the 2007 Amendments did not alter that responsibility, when we assume, as we must, that "Congress is aware of existing law when it passes legislation." *South Dakota v. Yankton Sioux Tribe*, 522 U.S. 329, 351 (1998) (quoting *Miles v. Apex Marine Corp.*, 498 U.S. 19, 32 (1990) (internal quotation marks omitted)).

[88] *Mensing*, 588 F.3d at 609.

information should be added, *it should provide adequate supporting information to FDA*, and FDA will determine whether the labeling for the generic and listed drugs should be revised."[59] Generic manufacturers must also follow the same record keeping and reporting of adverse drug experiences postmarketing as name brand manufacturers. As the FDA explained, "ANDA applicants [must] submit a periodic report of adverse drug experiences even if the ANDA applicant has not received any adverse drug experience reports *or initiated any labeling changes*."[60] At the very least, then, the FDA contemplates that generic manufacturers will initiate label changes in addition to echoing changes to the name brand label.

Nevertheless, Actavis points out that 21 U.S.C. § 355(e) "authorizes the withdrawal of approval of an application if 'there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof.' This provision applies to both [generic] and [listed] drug products."[61] Further, 21 C.F.R. § 314.150, explains that the FDA will initiate proceedings to withdraw approval for a generic drug if "the labeling for the drug . . . *is no longer consistent with* that for the listed drug . . . except for differences approved in the

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[59] 57 Fed. Reg. 17950, 17961 cmt. 40 (Apr. 28, 1992) (emphasis added).

[60] 57 Fed. Reg. 17950, 17965 cmt. 53 (Apr. 28, 1992) (emphasis added).

[61] 57 Fed. Reg. at 17962 (quoting 21 U.S.C. § 355(e)).

ANDA . . . ."[62] Actavis reads this language to prevent it from revising the label of its generic metoclopramide, because doing so would result in the FDA's withdrawal of approval.

The FDA promulgated § 314.150 in response to comments that it "should create a new provision authorizing the agency to withdraw an [ANDA] if the [ANDA] holder failed to modify its labeling to match labeling changes in the reference listed drug."[63] After being "revised . . . accordingly," the final version now "states that the ANDA applicant's failure to maintain drug labeling that is consistent with that of the listed drug may be grounds for withdrawing approval of the [ANDA]."[64]

Similarly, in response to a comment that the "FDA should create a mechanism to compel ANDA holders to revise their labeling to conform to the listed drug product once the ANDA is approved," the FDA observed that 21 U.S.C. § 355(e)(2) already "authorizes the withdrawal of approval of an application if 'there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in [its] labeling.'"[65] Because this provision applies to both listed and generic drug products and "an ANDA must have labeling that is the same as the

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[62] 21 C.F.R. § 314.150(b)(10) (emphasis added).

[63] 57 Fed. Reg. at 17970 cmt. 78.

[64] *Id.*

[65] 57 Fed. Reg. 17950, 17961 (quoting 21 U.S.C. §355(e)(2)).

. . . listed drug," the FDA explained that "a generic drug . . . whose labeling is inconsistent with the listed drug's labeling might not be considered safe and effective."[66] Given that, the FDA crafted § 314.150 "to permit the agency to withdraw approval of the ANDA if an applicant fails to maintain labeling in compliance with the requirements of the" Hatch-Waxman Amendments.[67]

The overarching import of these remarks suggests, as one district court put it, that "the purpose of [the] regulation was not to prevent a generic manufacturer from improving or strengthening its warnings. It was, instead, to ensure that the FDA could require a generic manufacturer to modify its labeling to match labeling changes in the reference listed drug."[68] In *Levine*, the Supreme Court found it "difficult to accept" that "the FDA would bring an enforcement action against a manufacturer for strengthening a warning."[69] Nor is "a drug . . . misbranded simply because the manufacturer has altered an FDA-approved label"; rather, the misbranding provisions concern the accuracy of the label's substance and the adequacy of its warnings and

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[66] *Id.*

[67] *Id.*

[68] *Bartlett*, ___ F. Supp. 2d. ____, 2009 WL 3126305, at *18 (quoting *Barnhill*, 2007 U.S. Dist. LEXIS 44718, at *13). *But see Mensing*, 562 F. Supp. 2d at 1062 (finding that this statement "underscore[s] the notion that the ANDA drug's label must remain the same as that of the listed drug").

[69] *Levine*, 129 S. Ct. at 1197.

the FDA "contemplates that federal juries will resolve most misbranding claims."[70]

This is not to say that generic drug manufacturers—or any drug manufacturers, for that matter—are free to make whatever changes they see fit. Most labeling modifications must be pursued through a "major changes" procedure, which requires prior FDA approval before any modification takes place.[71] As the *Levine* Court observed, "[g]enerally speaking, a manufacturer may only change a drug label after the FDA approves a supplemental application."[72] A manufacturer may, however, "make certain changes to its label before receiving the agency's approval," through the so-called "changes being effected," or CBE, process delineated in 21 C.F.R. § 314.70(c)(iii).[73]

Accordingly, Demahy posits that Actavis could have complied with FDA regulations and state law by using either the CBE process, the "major changes" procedure (otherwise known as the prior approval process), or a third method—warnings sent directly to healthcare providers. A finding of preemption would require that all be foreclosed to generic manufacturers. We consider each in turn.

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[70] *Levine*, 129 S. Ct. at 1197; *see also* 21 U.S.C. § 355(e).

[71] 21 C.F.R. § 314.70(b)(2)(v); 21 U.S.C. § 356a(c)(1).

[72] 129 S. Ct. at 1196.

[73] *Id.*

A. The "Changes Being Effected" Process

Where, as here, the requisite labeling change would "add or strengthen a contraindication, warning, precaution, or adverse reaction,"[74] to reflect "information not previously submitted to the [FDA]" and is based on "sufficient evidence of a causal association," it qualifies for the CBE process,[75] meaning the manufacturer "may make the labeling change upon filing its supplemental application with the FDA; it need not wait for FDA approval."[76] The district court focused much of its analysis on the availability of the CBE process to generic manufacturers.

"Just as nothing in the text of the Hatch-Waxman Amendments forbids a generic manufacturer from changing its drug's label from the listed version's

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[74] *Id.* (quoting 21 C.F.R. § 314.70(c)(6)(iii)(A)) (internal quotation marks omitted).

[75] 73 Fed. Reg. 49603, 49604 (2008) ("Expressly requiring that a CBE supplement reflect newly acquired information and be based on sufficient evidence of a causal association will help to ensure that scientifically accurate information appears in the approved labeling for such products."); 21 C.F.R. § 601.12(f)(2) (explaining that the CBE is available only when the proposed change "reflect[s] newly acquired information"); 21 C.F.R. § 314.70(c)(6)(iii)(A) (requiring that a CBE be supported by "evidence of a causal association[that] satisfies the standard for inclusion in the labeling under 201.57"); 21 C.F.R. § 814.3(o) (defining "[n]ewly acquired information" as "data, analyses, or other information not previously submitted to the agency").

[76] *Levine*, 129 S. Ct. at 1196 (quoting 21 C.F.R. § 314.70(c)(6)(iii)(A)).

post-approval,"[77] the CBE regulation also does not, on its face, distinguish between generic and name brand drug manufacturers; that is, it does not forbid a generic manufacturer from using the CBE process to unilaterally change a label. Located at 21 C.F.R. § 314.70, the regulation provides that "the holder of an approved application"—not just an approved new drug application—"may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change."[78]

Unsupported by the regulation's text, then, Actavis must seek support from FDA commentary for its argument that generic manufacturers cannot use the CBE process. Specifically, when the Agency revised the CBE regulation following the Hatch-Waxman Amendments, it reminded "ANDA applicants that, as noted in paragraph 4 above, the labeling for an ANDA product must, with few exceptions, correspond to that for the reference listed drug."[79]

At first glance, this provision seems to provide arguable support for Actavis's view: the comment, unlike others it cites, refers to "the labeling for an ANDA *product*," rather than "the labeling proposed for a product in an ANDA *application*" and thus could be read to mandate that a generic's labeling remain the "same as" the listed drug's after approval. A closer examination—one that accounts for the comment's reference to "paragraph 4"—indicates, however, that

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[77] *Bartlett*, 2009 WL 3126305 at *14.

[78] 21 C.F.R. § 314.70(c)(6).

[79] 57 Fed. Reg. at 17955.

the FDA's explanation was still fixed on the pre-approval label.

"Paragraph 4" turns down a suggestion that the FDA "accept ANDA's with warnings or precautions in addition to those on the reference listed drug's label," by noting that "the applicant's *proposed labeling* [must] be the same as that of the listed reference drug" with exceptions not relevant here.[80] So, once again we encounter an admonition that the content of a generic drug's labeling during the ANDA approval process conform to that of the corresponding listed drug; there is no direction, however, as to what may happen *afterwards*. It would be a stretch then, in light of paragraph 4's cameo in the FDA's comment to the CBE regulation, to read it as Actavis would have us do, and expand the directive that "the labeling proposed for the drug [be] the same as the labeling approved for the listed drug," into the post-approval period, an undemanded play with displacement of traditional state regulation.[81]

In addition, these comments accompanied the only change that the FDA made to the CBE regulations when implementing the Hatch-Waxman Amendments: the addition of a paragraph requiring applicants to "comply with the patent information requirements under [21 U.S.C. §355(c)(2)]."[82] Actavis's preferred reading of these comments is not plausible unless we

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[80] *Id.* at 17953.

[81] 21 U.S.C. § 355(j)(4)(G).

[82] 57 Fed. Reg. at 17983 (later codified at 21 C.F.R. § 314.70(e) (1993)).

accept the proposition that the FDA would, in a minor and unrelated revision, express the novel view that generic manufacturers are altogether forbidden from using the CBE process.

On the other hand, what the FDA clearly did do to implement Hatch-Waxman cuts against Actavis's position, or at the very least muddies congressional and agency intent: it promulgated 21 C.F.R. § 314.97, entitled "Supplements and other changes to an approved abbreviated application."[83] This rule provides that ANDA applicants "shall comply with the requirements of §§ 314.70 and 314.71 regarding the submission of supplemental applications and other changes to an approved abbreviated application."[84] The requirements of § 314.70 include, of course, the CBE process.

Had the FDA intended to deny generic manufacturers access to the CBE procedures, notwithstanding § 314.97's plain language, we might expect the FDA to say so, either in § 314.97 or in the CBE provision itself. If this was the FDA's intent—and the industry's understanding at the time—it passed over the opportunity to make that clear in these provisions promulgated in Hatch-Waxman's wake. As the regulations stand, however, we cannot tack the words "only when a listed drug manufacturer has first

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[83] 57 Fed. Reg. at 17987. The FDA received no comments on this change.

[84] 21 C.F.R. § 314.97. We acknowledge that the CBE regulations appear at 21 C.F.R. § 314.70, which is located in Subpart B of Part 314. The FDA entitled Subpart B "Applications," while giving Subpart C the moniker "Abbreviated Applications."

revised its label" onto the end of § 314.97—as Actavis's argument begs.

Nonetheless, Actavis insists that the CBE process is only available to generic manufacturers to implement changes already made to the name brand's label: in other words, that § 314.97 only requires that generics *follow* name brand labeling if and when a change is made by the name brand manufacturer. For that reason, Actavis says, the FDA rejected a comment suggesting that ANDA holders be required to submit drug labeling at periodic intervals to ensure that the generic label matched its listed counterpart. The FDA found such a procedure unnecessary because "existing reporting requirements at 21 C.F.R. § 314.70 [including the CBE provision] ensure that labeling changes are brought to FDA's attention in an appropriate and timely fashion."[85] The FDA will then "advise ANDA holders of changes to be made after approval, but postapproval changes resulting from the expiration of exclusivity or patent protection are the responsibility of the ANDA holder."[86] While this comment surely indicates that a generic drug manufacturer should use the CBE process to enact changes endorsed by the FDA, it does not say, however, that the process was not also intended to allow ANDA holders to act independently from the name brand manufacturers.

Actavis also directs us to the FDA's rejection of yet another comment as part of administrative

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[85] 57 Fed. Reg. at 17961 cmt. 39.

[86] *Id.*

implementation of Hatch-Waxman. This time, it is one that suggested empowering "ANDA applicants to deviate from the labeling for the reference listed drug to add contraindications, warnings, precautions, adverse reactions, and other safety-related information.[87] In response, the FDA reiterated that "the ANDA product's labeling must be the same as the listed drug's product labeling because the listed drug product is the basis for ANDA approval."[88] Because "[c]onsistent labeling will assure physicians, health professionals, and consumers that a generic drug is as safe and effective as its brand-name counterpart," the FDA instructed "an ANDA applicant [who] believes new safety information should be added to a product's labeling . . . [to] contact FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised."[89]

Nothing in this response deviates from the now-familiar distinction between the near-unqualified ban on labeling differences pre-approval and their availability "after approval of an ANDA." During that latter period, "if an ANDA holder believes that new safety information should be added, it should provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised."[90]

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[87] 57 Fed. Reg. at 17961 cmt. 40.

[88] *Id.*

[89] *Id.*

[90] *Id.*

Actavis maintains that this passage demonstrates that, for generic drugs, the FDA "decides whether a revision is necessary, not the drug manufacturer." We agree, but the FDA is the ultimate arbiter for *all* changes—whether prompted by a pioneer manufacturer or a generic one. *Every* submitted change requires FDA approval, even one that takes effect immediately through the CBE process. The FDA makes these approval decisions "based on a comprehensive scientific evaluation of the product's risks and benefits under the conditions of use prescribed, recommended, or suggested in the labeling."[91] Through this review, the FDA is in effect and in fact "determin[ing] whether the labeling for the generic and listed drugs should be revised." This is no less true when the FDA reviews the change only after it has been made, as is the case with CBE changes. At best, then, this language is reason for pause, not for a conclusive reading, or a finding of impossibility preemption.

Lastly, Actavis emphasizes the FDA's recent statements suggesting that generics cannot use the CBE process and that federal law preempts state-law failure-to-warn claims brought against generics. Actavis first points to two amici briefs filed by the FDA in *Colacicco v. Apotex Corp.*, a case heard in the Eastern District of Pennsylvania[92] and then in the Third Circuit.[93] The briefs argued that Hatch-Waxman and implementing FDA regulations preempt state

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[91] 73 Fed. Reg. at 49604.

[92] *Colacicco v. Apotex, Inc.*, 432 F. Supp. 2d 514 (E.D. Pa. 2006).

[93] *Colacicco v. Apotex, Inc.*, 521 F.3d 253 (3d Cir. 2008).

failure-to-warn claims as to both listed and generic drug manufacturers.[94] In so doing, the FDA took the position that generic manufacturers could not utilize the CBE process at all.[95] The Third Circuit found the plaintiffs' failure-to-warn claims preempted.[96] The Supreme Court later decided *Levine*, and in light of that holding, granted certiorari in *Colacicco*, vacated the judgment of the Third Cicruit, and remanded for further consideration.[97] In response to *Levine*, the United States withdrew as amicus in *Colacicco* and notified the Third Circuit that the United States "does not take a position on whether [the state-law failure-to-warn claims] are preempted" and "has not yet conducted an examination of various preemption issues following the Supreme Court's decision in *Wyeth* [*Levine*] that would be necessary to inform a position of the United States in this case."[98] Now withdrawn, the FDA's amicus views are muted and we do not consider them.

Similarly, Actavis has recently lost another pillar of support. In its briefs, Actavis relies on a footnote in the

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[94] Brief of United States as *Amicus Curiae*, *Colacicco v. Apotex, Inc.*, C.A. No. 05-5500-MMB (E.D. Pa. filed May 10, 2006); Brief of United States as *Amicus Curiae*, *Colacicco v. Apotex, Inc.*, No. 06-3107 (3d Cir. filed Dec. 4, 2006).

[95] *Id.* at 7–8, 18

[96] *Colacicco*, 521 F.3d at 276.

[97] *Colacicco v. Apotex*, No. 08-437 (Mar. 9, 2009).

[98] Letter from Sharon Swingle, U.S. Department of Justice - Civil Division, Appellate, to Marcia M. Waldron, Clerk, United States Court of Appeals for the Third Circuit (Apr. 28, 2009).

FDA's proposed 2008 revision to the CBE regulations, which states that "CBE changes are not available for generic drugs approved under an ANDA under 21 U.S.C. 355(j). To the contrary, a generic drug manufacturer is required to conform to the approved labeling for the listed drug."[99] But the final version of the rule omits this footnote's language. In fact, the final rule—which seeks to "affirm that a CBE supplement is appropriate . . . only to reflect newly acquired information . . . and [when] there is sufficient evidence of a causal association with the drug"—is virtually silent as to generics altogether.

The final rule does, however, specifically note that the FDA is "amending its regulations regarding changes to an approved [name brand] application."[100] Noting this statement, Actavis points out that the rule does not mention that the changes affect generic applications as well. It then posits that this omission is a sign that the CBE process simply does not apply to generics.

We might agree absent three salient insights. First, in its commentary to the final version of the regulation, the FDA removed the footnote that explicitly stated what Actavis asks this court to now hold: that the CBE process does not apply to generics. Second, these regulations were promulgated prior to the Supreme Court's decision in *Levine* and since that time, the FDA has withdrawn its amicus in *Colacicco*, as part of an apparent reconsideration of its

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[99] 73 Fed. Reg. at 2849 n.1.

[100] 73 Fed. Reg. at 49604.

preemption position. Lastly, the 2008 final rule mentions generics only once—in a citation after a sentence that reads: "The agency has clarified by regulation and guidance the types of supplements that should be filed to satisfy a sponsor's obligations to change a drug's labeling . . . ." In support of this statement, the FDA cites 21 C.F.R. § 314.70 (which contains the CBE regulation) and a document entitled "Guidance for Industry: Changes to an Approved NDA or ANDA," produced in November 1999. The guidance document notes that "[a]ll labeling changes for ANDA products must be consistent with [21 U.S.C. § 355(j)]," but otherwise does not distinguish between label changes made by pioneer manufacturers and their generic counterparts.[101]

Without explicit reference to the use of the CBE process by generic manufacturers, we decline to read in a bar to its use. The FDA's "earlier position," either as amicus or commentator, is instead "deprived of all claim to deference, by the fact that it is no longer the agency's position."[102]

B. Prior Approval Process

Nor does anything in the FDCA or Hatch-Waxman Amendments explicitly forbid generic manufacturers from proposing a label change through the so-called

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[101] Guidance for Industry: Changes to an Approved NDA or ANDA, at *24 (November 1999). The guidance document refers to section 505(j) of the FDCA, which is codified at 21 U.S.C. § 355(j).

[102] *Riegel v. Medtronic, Inc.*, 128 S. Ct. 999, 1009 (2008).

prior approval process.[103] While FDA regulations provide for permissive use of the CBE process for warning enhancements, and the prior approval process is required for "major changes," there is no indication of an agency policy, let alone congressional intent, to prevent generic manufacturers from proposing any and all labeling changes—no matter the significance of the change—through the prior approval process. Rather, the regulations governing labeling changes repeatedly use the nonrestrictive phrase "[t]hese changes include, but are not limited to" in describing the changes manufacturers may propose through each type of supplement.[104] Indeed, manufacturers are *required* to use the prior approval process for most "labeling changes."[105]

C. "Dear Doctor" Letters

In addition to the CBE and prior approval processes, Demahy posits that Actavis could have satisfied its state-law duty to warn by communicating directly with doctors, through a "Dear Doctor" letter. These letters—addressed to medical professionals and intended to explain the risks associated with prolonged use of metoclopramide—would also be subject to FDA regulation because they fall within the agency's broad definition of "labeling."[106] But, when promulgating its

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[103] 21 C.F.R. § 314.70(b)(2)(v)(A).

[104] *Id.* at §§ 314.70(b)(2), (c)(2), (d)(2).

[105] *Id.* at § 314.70(b)(2)(v)(A).

[106] 21 C.F.R. §§ 202.1(1), (2); *see also* 21 C.F.R. § 200.4 (regulating content and appearance of mailings about drugs to physicians).

labeling regulations well before the Hatch-Waxman Amendments, the FDA made clear that the requirements "do not prohibit a manufacturer . . . from warning health care professionals whenever possibly harmful adverse effects associated with the use of the drug are discovered."[107]

Thus, though generic manufacturers cannot send "Dear Doctor" letters without prior FDA approval, they can suggest that the FDA send such letters on their behalf;[108] the FDA will then send letters out if it determines that they are a necessary part of a risk evaluation and mitigation strategy.[109] Under Louisiana law, a drug manufacturer may discharge its duty to warn through notice to the prescribing physician.[110]

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[107] 44 Fed. Reg. 37434, 37447 (June 26, 1979).

[108] 21 U.S.C. § 355-1(i)(2) (establishing this process as part of the 2007 amendments to the FDCA). Although this process was not in effect when Demahy took metoclopramide, the FDA's later endorsement of it provides support for Actavis's contention that Congress did not intend that generic manufacturers send out "Dear Doctor" letters independently. Although "[o]ccasionally, drug manufacturers and distributors mail important information about their drugs to health care professionals" with or without FDA involvement, longstanding FDA instructions for these mailings are directed at pioneer drug companies. NDAs: "Dear Healthcare Professional" Letters (July 2, 2003), *available at* http://www.fda.gov/cder/mapp/6020.10.pdf.

[109] *Id.*

[110] *See Stahl v. Novartis Pharm. Corp.*, 283 F.3d 254, 266 (5th Cir. 2002) (applying Louisiana law); *see also Marks v. OHMEDA, Inc.*, 2003-1446, p. 11 (La. App. 3 Cir. 3/31/04), 871 So. 2d 1148, 1157; *Mikell v. Hoffman-LaRoche, Inc.*, 94-0242, pp. 7–8 (La. App. 1 Cir. 12/22/94); 649 So. 2d 75, 79–80.

Of the three avenues for complying with both state and federal law that Demahy identifies—the CBE process, the prior approval process, and letters sent directly to healthcare providers—each shares the same fundamental attributes: the manufacturer bears primary responsibility for maintaining its label consistent with safe and effective use of its product; when reports indicate that a label requires revision, the manufacturer must alert the FDA and provide supporting scientific data; and the FDA then makes the decision whether such a labeling change is supported by science. Even though with the CBE process, the decision is made after the label has been changed, the key feature remains: the FDA is still the final arbiter of labeling changes, while the manufacturer retains primary responsibility for the content of its label. The federal interest is in maintaining safe and effective labeling that is consistent across name brand and generic bioequivalent versions of the same drug. *Who* prompts the FDA to consider necessary changes to that shared label is immaterial.

At best, Actavis has demonstrated that even an interpretation of the CBE process most favorable to Actavis (and one that fails to persuade this court) is decidedly equivocal. Yet, equivocation falls short of the "clear and manifest purpose of Congress" required for a finding of preemption.[11] Even assuming that the CBE regulation cannot be used by an ANDA holder to amend its label without FDA pre-approval, *Levine*'s

[11] *Levine*, 129 S. Ct. at 1195 (quoting *Lohr*, 518 U.S. at 485).

principles still apply with full force, and we agree with Demahy that generic drug manufacturers may use two other means of complying with both federal and state law—the prior approval process and correspondence sent directly to healthcare providers.

Though most courts to have considered the question—including the one below—focus on the CBE process, the CBE regulation was not the exclusive, or even the primary, basis for rejecting preemption in *Levine*. Rather, the Court explained that the brand name drug manufacturer's quest for preemption was grounded in a "more fundamental misunderstanding" of the regulatory regime: that the "FDA, rather than the manufacturer, bears primary responsibility for drug labeling."[112] As we have seen, the opposite is true: "a central premise of federal drug regulation [is] that the manufacturer bears responsibility for the content of its label at all times."[113]

Actavis urges that Congress intended to preempt state law because FDA regulations do not impose a duty on generic manufacturers to change their drug labels. This argument does not address the question we must answer. Preemption is not found because state law imposes duties and federal law does not. We look instead to the state-law imposition of duties, and to whether those duties make simultaneous compliance with federal law impossible. What the FDA might have done once Actavis suggested these changes is immaterial to the imposition of liability; *Levine*

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[112] *Id.* at 1197.

[113] *Id.* at 1197–98.

makes plain that uncertainty about the FDA's response makes federal preemption less likely: "absent clear evidence that the FDA would not have approved a change to [the drug's] label, we will not conclude that it was impossible for the [the manufacturer] to comply with both federal and state requirements."[114] The record here contains nothing, let alone "clear evidence," that suggests the FDA would have rejected a labeling proposal from Actavis. In fact, as discussed, the FDA mandated earlier this year that manufacturers of metoclopramide revise their labels to disclose further risks of tardive dyskinesia associated with long-term use.[115]

Finally, Actavis's use of Justice Breyer's concurrence in *Levine* is here unavailing: he said *if* an agency sets a floor and a ceiling, its actions may very well enjoy preemptive effect. No such regulation bearing the force of law is before us, while the FDA's retreat from its earlier position on preemption and the use of the CBE provision casts further doubt on Actavis's argument. That being said, had the FDA gone further than Justice Breyer would require and specifically examined the risk of long-term use of metoclopramide at the time that Demahy's cause of action arose, the argument for preemption would be on surer footing.[116]

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[114] *Id.* at 1198.

[115] Letter from Joyce Korvick, Deputy Dir. for Safety, Div. of Gastroenterology Products, Center for Drug Evaluation and Research, FDA, to NDA holders for Reglan, at 3 (Feb. 26, 2009)

[116] *See Dusek v. Pfizer, Inc.*, No. Civ. A. H-02-3559, 2004 WL 2191804, at *10 (S.D. Tex. Feb. 20, 2004) (unpublished) ("The

VI

Even if compliance with state and federal law is not "impossible," state law is nonetheless preempted if it stands as an "obstacle to the accomplishment and execution of the full purposes and objectives of Congress" as embodied in the Hatch-Waxman Amendments and the FDCA.[117] Here, if preemption is to be found, two additional conclusions necessarily follow: first, that Congress intended the name brand drug manufacturer to bear the sole burden of coping with incipient risks, even when it has ceased manufacturing the drug and left the market to generics; and two, that Congress intended either that the name brand manufacturer be liable for *all* failure-to-warn claims—even those arising out of the use of generic substitutes—or, that the injured

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Court does not hold that FDA drug approvals in general preempt failure to warn claims. The Court merely rules that permitting Plaintiffs' claim would be authorizing judicially what the FDA already has expressly disallowed. . . . In the face of numerous contentions from several different sources that [the drug] should contain a warning that [it] can cause suicide, the FDA has consistently determined no such explicit causation admonition is justified scientifically. . . . Therefore, on the specific facts of this case . . ., Plaintiffs' failure to warn claim is preempted because it is in direct, actual conflict with federal law."). *Cf. Perry v. Novartis Pharm. Corp.*, 456 F. Supp. 2d 678, 686–87 (E.D. Pa. 2006) (relying on the fact that the FDA had made no conclusive determination on the specific risk and label at issue, prior to the time the cause of action arose, in holding that the plaintiff's failure-to-warn claim was not preempted). *See generally* Catherine M. Sharkey, *Products Liability Preemption: An Institutional Approach*, 76 GEO. WASH. L. REV. 449, 513–20 (2008) (advocating for the approaches taken in *Dusek* and *Perry*).

[117] *Crosby*, 530 U.S. at 372–73.

plaintiff be left with no remedy. In assessing congressional objectives, these corollaries cannot be put aside.

Compliance with Louisiana's failure-to-warn law, so says Actavis, will necessarily burden generic manufacturers with duplicative studies, trials, and other data-gathering exercises, all putative prerequisites to placing generic companies on notice that label changes are warranted. These burdens, if imposed, would no doubt drive up the development costs, and thus, the market price, of generic drugs—thwarting a key tenet of Hatch-Waxman "to make available more low cost generic drugs by establishing a generic drug approval procedure."[118]

But what Louisiana law would require of generic drug companies does not inevitably impose significant investment of time and money. For one, Actavis fails to identify any statutory or regulatory provision that obligates manufacturers to justify labeling changes through their own clinical trials or other similarly onerous efforts.[119] Yes, requests to the FDA for label changes must be buttressed with scientific evidence, but nothing indicates that the evidence must be—as a matter of regulatory prescription or scientific reliability—acquired through the manufacturer's own clinical tests. As FDA regulations make plain, the regulatory regime contemplates that drug companies will effect labeling changes without conducting new

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[118] H.R. Rep. No. 98-857, pt. 1, at 14, 1984 U.S.S.C.A.N. at 2647.

[119] *See* 21 U.S.C. § 356a (containing no such requirement); 21 C.F.R. § 314.70 (same); *see also Bartlett*, 2009 WL 3126305, at *24 (noting the absence of any such requirement).

clinical trials: "labeling shall be revised to include a warning as soon as there is reasonable evidence of a serious hazard with a drug; *a causal relationship need not have been proved*."[120] The FDA expects that such "reasonable evidence" might be derived from, among other sources, "new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses)."[121] While clinical studies, then, *may* be used to support labeling changes, they are in no way prerequisites to those changes. When the FDA itself mandated an enhanced warning for metoclopramide in early 2009, it did not conduct its own studies, but referenced studies published elsewhere.

Actavis concedes that generic manufacturers already must report "each adverse drug experience that is both serious and unexpected . . . as soon as possible but in no case later than 15 calendar days of initial receipt of the information by the applicant,"[122] and every other "adverse drug experience . . . at quarterly intervals, for 3 years from the date of

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[120] 21 C.F.R. § 201.80(e); *see also* 21 C.F.R. § 314.70(c)(6)(iii) (a CBE may be used "[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling under [21 C.F.R.] § 201.57(c)"); *Id.* at § 201.57(c)(6) (explaining that evidence must be "reasonable" in order to change a label's warnings and precautions); *Id.* at § 201.57(c)(7) (explaining that there must be "some basis to believe" in order to change a label's discussion of adverse reactions).

[121] 73 Fed. Reg. at 49604.

[122] 21 C.F.R. § 314.98 (referencing § 314.80); *Id.* at § 314.80 (c)(1)(i).

approval . . . and then at annual intervals."[123] The FDA also requires that generics "develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA."[124] In *Levine*, the Supreme Court found that multiple reports of adverse drug experiences provided the substantiation necessary to justify a request for a heightened warning.[125]

At least in the case of metoclopramide, it seems, the allegedly higher risk of long-term use was noted in medical literature beginning in the 1980s and 1990s.[126] Even if state law prompts Actavis to alert the FDA to this information, Actavis has provided no evidence that such collection and analysis of existing data and conclusions would result in significant additional expenditures.

Stepping back, the duty to warn is, in general terms, predicated on the superior knowledge of the manufacturer.[127] In the world of prescription drugs, a pharmaceutical company manufactures, and the FDA approves, a branded drug only after extensive research and testing. Pioneer drug manufacturers thus develop

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[123] 21 C.F.R. § 314.80(c)(2)(i).

[124] 21 C.F.R. § 314.80(b).

[125] *Levine*, 129 S. Ct. at 1197.

[126] *See, e.g.*, *Kelly v. Wyeth*, 2007 WL 1302589, at *2 n.7 (Mass. Super. 2007).

[127] *See, e.g.*, *Greenman v. Yuba Prods., Inc.*, 377 P.2d 897 (Cal. 1963); MATTHEW BENDER 1-6 PRODUCTS LIABILITY PRACTICE GUIDE § 6.03(4)(c).

superior knowledge of their product, and the duty to warn is more fairly imposed, as it was in *Levine*. Conversely, generic manufacturers undertake limited research efforts thanks to Hatch-Waxman. They can obtain approval for their copycat drug and label with the limited showing that their product is the "same as" a branded drug. Consistency among generic and name brand manufacturers not only avoids redundant research and monitoring efforts, it also assures consumers and physicians that the generic product is safe and effective.[128]

That difference in initial regulatory burdens marks a stark tension between Hatch-Waxman's quest to quickly and cheaply place generic drugs on the market and a state law tort regime that represents the lone remedy for individuals harmed by inadequate labeling of generic drugs. Nevertheless, Congress did not consider the Hatch-Waxman Amendments in a vacuum, as Actavis would have us do now. Instead, the Amendments serve as just that—amendments—to the FDCA and to the modern regulatory regime governing all prescription drugs that the FDCA first established. Hatch-Waxman's goals are thus tethered to those of the overall regulatory scheme—chief among them the maintenance of safety and efficacy. In this wider context, nothing about the Hatch-Waxman Amendments, and their goal of cheaper drugs, obviates the concomitant prescription that all drugs, even cheaper ones, remain safe. Instead, as *Levine* explains,

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[128] *Changes in the Labeling of ANDAs Subsequent to Revision of Innovator Labeling*, U.S. Department of Health and Human Services, Food and Drug Administration, Division of Generic Drugs, Policy and Procedure Guide 38-89, Aug. 21, 1989.

"failure-to-warn actions . . . lend force to the FDCA's premise that manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times."[129] "The FDA has limited resources to monitor the 11,000 drugs on the market, and manufacturers have superior access to information about their drugs, especially in the postmarketing phase as new risks emerge."[130] In passing the FDCA, Congress "determined that widely available state rights of action provided appropriate relief for injured [drug] consumers" and that "state-law remedies further consumer protection by motivating manufacturers . . . to give adequate warnings."[131] We see no reason why the same cannot be said for the Hatch-Waxman Amendments to the FDCA.

Today's inquiry does not concern the propriety of state failure-to-warn claims. It is enough that such a claim exists; we cannot consider whether a patient—as a policy matter—should have a state-law claim for a drug manufacturer's alleged failure to adequately warn of its products' risks. Louisiana says that she should. We have examined evidence that Congress believed she should not. In this case, unless the law would somehow harness liability onto name brand manufacturers for all failure-to-warn claims, preemption in this case would leave Demahy without a remedy. Yet, "[i]f Congress had intended to deprive [Demahy] of a long available form of compensation, it surely would have expressed that intent more

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[129] *Levine*, 129 S. Ct. at 1202.

[130] *Id.*

[131] *Id.* at 1199–1200.

clearly."[132] To hold otherwise would leave us with the bizarre conclusion that Congress intended to implicitly deprive a plaintiff whose doctor prescribes a generic drug of *any* remedy, while under *Levine*, that same plaintiff would have a state-law claim had she only demanded a name brand drug instead.

Our review of the applicable statutes and regulations has not provided evidence sufficient to overcome the presumption against preemption; that is, there is no evidence sufficient for us to say that it was the "clear and manifest purpose" of Congress to preempt state law, or to allow the FDA to do the same.[133] The presumption reflects the judiciary's reluctance to find the intention of a coordinate federal branch to supplant state law. The preservation of our federalism requires Congress to do more than it—or the FDA—has chosen to do here. We cannot make the choice for them. The need for supplanting state duties here and the attendant calibration of costs and benefits are far beyond judicial ken—a reality reflected in the legal demands of conflict preemption and not wholly distant from the demands for implications of private rights of action.

Because state imposition of duties to warn on generic drug manufacturers neither renders compliance with federal regulation impossible nor obstructs the goals of that regulation, we AFFIRM the district court's finding that Demahy's state-law failure-to-warn claims are not preempted.

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[132] *Bates*, 544 U.S. at 449.

[133] *Levine*, 129 S. Ct. at 1195.

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PETITIONER'S BRIEF

Nos. 09-993, 09-1039, and 09-1501

IN THE

Supreme Court of the United States

PLIVA, INC., ET AL.,
Petitioners,
v.
GLADYS MENSING,
Respondent.

ACTAVIS ELIZABETH LLC,
Petitioner,
v.
GLADYS MENSING,
Respondent.

ACTAVIS INC.,
Petitioner,
v.
JULIE DEMAHY,
Respondent.

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QUESTION PRESENTED

Are the states preempted under the Supremacy Clause of the Constitution from requiring additional safety information on a generic product label where the brand has not changed its label?

LIST OF PARTIES

Nos. 09-993 and 09-1039 (Eighth Circuit)

A. **Defendants-Appellees**

PLIVA, Inc.

Teva Pharmaceuticals USA, Inc.

UDL Laboratories, Inc.

Actavis Elizabeth LLC

Wyeth, LLC

B. **Plaintiff-Appellant**

Gladys Mensing

No. 09-1501 (Fifth Circuit)

A. **Defendant-Appellant**

Actavis Inc.

B. **Plaintiff-Appellee**

Julie Demahy

CORPORATE DISCLOSURE STATEMENT

Actavis Group hf is a privately-held Icelandic company, and the parent corporation of Actavis Group PTC, ehf, which is the parent of petitioner Actavis Inc., a Delaware corporation. Petitioner Actavis Elizabeth LLC, a subsidiary of Actavis Inc., is the successor to Purepac Pharmaceutical Co. No publicly held corporation owns ten percent or more of Actavis Inc.'s stock.

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BRIEF OF PETITIONER ACTAVIS

OPINIONS BELOW

The opinion of the Eighth Circuit Court of Appeals is reported at 588 F.3d 603 (8th Cir. 2009) and reprinted in the Joint Appendix (JA) at 100-21. The district court's opinion is reported at 562 F. Supp. 2d 1056 (D. Minn. 2008) and reprinted at JA 364-85.

The opinion of the Fifth Circuit Court of Appeals is reported at 593 F.3d 428 (5th Cir. 2010) and reprinted at JA 520-63. The district court's opinion is reported at 586 F. Supp. 2d 642 (E.D. La. 2008) and reprinted at JA 477-519.

JURISDICTION

This Court has jurisdiction under 28 U.S.C. § 1254.

The Court of Appeals for the Eighth Circuit rendered its decision in Nos. 09-0993 and 09-1039 on November 27, 2009. The petitions for writ of certiorari were filed on February 19 and 25, 2010, respectively.

The Court of Appeals for the Fifth Circuit rendered its decision in No. 09-1501 on January 8, 2010. The petition was filed timely on June 7, 2010, following an order extending the deadline.

CONSTITUTIONAL, STATUTORY AND REGULATORY PROVISIONS INVOLVED

The pertinent provisions of the United States Constitution, Article VI, clause 2, 21 U.S.C. § 355 and 21 C.F.R. §§ 314.3, 314.70, 314.94, 314.97 and 314.150 are reproduced in the Appendix to the Petition in 09-1501 at App. 113a-131a.

STATEMENT OF THE CASE

Congress created the modern generic drug industry when it amended the Federal Food, Drug, and Cosmetic Act (FFDCA) in 1984. Pub. L. No. 98-417, 98 Stat. 1585 (1984). In addition to streamlining the approval process for generic drugs, the legislation promoted confidence in their safety and effectiveness by ensuring that generic drugs were exact copies of their brand counterparts. In these consolidated cases, respondents seek to hold petitioners Actavis Inc. and Actavis Elizabeth LLC (collectively Actavis) and three other generic drug companies liable under state law for not adding safety information to the labels of their metoclopramide products.

Following this Court's decision in *Wyeth v. Levine*, 129 S. Ct. 1187 (2009) (*Wyeth*), numerous lower courts have held that generic manufacturers may be held liable for failing to add warnings to the labels of their products, contrary to the requirement that their labels duplicate the label of the brand drug. Unlike the brand manufacturer in *Wyeth*, generic manufacturers are prohibited from making

unilateral changes to their labels due to the same labeling requirement in the FFDCA and FDA's regulations. Respondents' state law claims would conflict with federal law by requiring Actavis to violate the same labeling requirement and are therefore preempted.

A. The Regulatory Framework.

1. New drugs.

Under the FFDCA, a new drug may not be marketed until the Food and Drug Administration (FDA) has approved a new drug application (NDA). 21 U.S.C. §§ 331(d), 355(a). Before an NDA is submitted, the manufacturer must conduct a range of preclinical investigations, obtain FDA authorization to conduct human clinical trials designed to establish safety and efficacy, and then conduct those clinical studies. 21 U.S.C. § 355(i); 21 C.F.R. § 312.20. Once all of these studies have been completed, the sponsor must submit an NDA containing "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective." 21 U.S.C. § 355(b)(1)(A). Because FDA will find a drug safe and effective only under labeled conditions of use, FDA must review the drug label as part of the NDA process. 21 U.S.C. § 355(a), (b)(1)(F), (c)(1)(A), (d).

After a drug is approved, the brand manufacturer's obligations continue. Manufacturers must maintain records, conduct additional testing as directed, and advise FDA of significant adverse health consequences that are reported following the

drug's introduction to the market. 21 U.S.C. § 355(k)(1); 21 C.F.R. § 314.80.

Further, as this Court held in *Wyeth*, when new information about the safety of a drug becomes apparent to the brand manufacturer, the brand manufacturer has the ability and obligation to change its label. 129 S. Ct. at 1198-99; *see also* 21 C.F.R. § 201.80(e). In order to make a labeling change, the brand manufacturer must file a supplemental application with FDA. 21 C.F.R. § 314.70. Although certain changes to a drug's approved labeling require prior approval, others, including changes to "add or strengthen a contraindication, warning, precaution or adverse reaction," may be made through the "Changes Being Effected" (CBE) process as soon as FDA receives the brand's supplemental application; the brand need not await FDA approval. 21 C.F.R. § 314.70(c)(6)(iii)(A)-(C).

In 2007, Congress added section 355(o)(4) to the FFDCA, which authorizes FDA to require labeling changes if it becomes aware of new safety information that it believes should be included in the labeling of the drug. 21 U.S.C. § 355(o)(4); Food and Drug Administration Amendments Act of 2007 (FDAAA), Pub. L. No. 110-85, § 901(a), 121 Stat. 823, 922-26 (2007). Prior to FDAAA, and during the period that is relevant to these cases, FDA had no authority to require a label change on a brand drug; it could only urge the manufacturer to amend its label.

2 Generic drugs

In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman) which streamlined the process by which companies may obtain approval of generic versions of brand drugs once the brand patents have expired. Pub. L. No. 98-417, 98 Stat. 1585 (1984). A principal goal of Hatch-Waxman was to achieve a "careful balance between promoting competition among brand names and 'generic' drugs," which would make safe and effective, low-cost drugs widely available, while "encouraging research and innovation" by extending patent protections for brand drugs.[1]

Unlike the brand sponsor, which must submit scientifically valid clinical trials demonstrating safety and efficacy in order to obtain approval, Hatch-Waxman permitted a generic applicant to rely on the safety and effectiveness information that the brand submitted if the generic applicant could demonstrate that its product is the same as the brand's product. 21 U.S.C. § 355(j)(2)(A); 21 C.F.R. § 314.94(a)(3). Part of the justification for Hatch-Waxman was FDA's conclusion that mandating generics to conduct the full testing required of the brand in order to market a drug was "unnecessary and wasteful," and that such testing could be "unethical" if patients in clinical trials were given placebos in place of drugs already proven effective.

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[1] *See* Abbreviated New Drug Application Regulations: Final Rule, 57 Fed. Reg. 17950, 17951 (April 28, 1992); H. R. Rep. No. 98-857, pt. 1, at 14 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647.

H.R. Rep. No. 98-857, pt. 1 at 16, *reprinted in* 1984 U.S.C.C.A.N. 2647, 2649.

Under Hatch-Waxman, FDA will approve a generic drug for marketing upon proof that the drug (1) has the same active ingredient(s) as, (2) has the same route of administration, dosage form and strength as, (3) *has the same labeling as*, and (4) is bioequivalent to, the brand drug. 21 U.S.C. § 355(j)(2)(A)(i)-(v) (emphasis added). In other words, the thrust of Hatch-Waxman is that the generic must demonstrate that its product is a copy of the brand in every significant respect, including its labeling, so that once approved the generic version can be substituted for the brand drug without a physician's intervention. *See* FDA, Approved Drug Products with Therapeutic Equivalence Evaluations, p. iv (30th ed. 2010).

The generic manufacturer is neither required to conduct the clinical studies needed to obtain approval of the brand product nor expected to master the clinical data that supports the various claims made on the product's label. Instead, the fundamental obligation of the generic manufacturer is to make a product that is a true copy of the brand. That obligation provides the framework for a generic drug manufacturer's regulatory duties.

A generic manufacturer is required to report adverse drug experiences that it "obtain[s] or otherwise receive[s]" from any source, including scientific literature, and to submit new safety information in its annual reports to FDA. *See* 21 C.F.R. § 314.98(a), (c); 21 C.F.R. § 314.80; 21 C.F.R.

§ 314.81(b)(2)(i). Nevertheless, the vast majority of such reports do not go to the generic manufacturer, but instead go directly to FDA or to the brand manufacturer.[2]

Generic drugs are required to have the same labeling as their brand counterparts. 21 U.S.C. § 355(j)(2)(A)(v); 21 C.F.R. § 314.94(a)(8)(iii). This means that generic drugs must have the same warnings as the brand. If the brand makes a labeling change, it is the generic manufacturer's responsibility to mirror that change in its own label. *See* FDA *Guidance for Industry, Revising ANDA Labeling Following Revision of the RLD Labeling* (May 2000) (ANDA Labeling Revision Guidance). If the brand does not make a labeling change, however, the generic manufacturer may not make a unilateral change to its own label. Making changes that render the generic label different from the label of the reference listed drug (the brand drug) is prohibited by the regulations that require the generic label to be the same as the brand label *at all times*. If a generic does not maintain the same label as the brand, FDA can remove the generic from the market. 21 C.F.R. § 314.150(b)(10).

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[2] *See* FDA Center for Drug Evaluation and Research, Handling of Adverse Experience Reports and Other Generic Drug Postmarketing Reports, *Manual of Policies and Procedures* 5240.8 (Nov. 1, 2000) ("Generally, [the Office of Generic Drugs] receives few AERs [adverse event reports] or similar reports.").

3 FDA's actions on metoclopramide

FDA approved the NDA for metoclopramide tablets, Reglan®, on December 30, 1980 for the treatment of diabetic gastroparesis.[1] It is the only drug currently approved by the FDA for this condition. Michael Camilleri, *Diabetic Gastroparesis*, 356 N. Eng. J. Med. 820, 827 (2007). In 1984, the Agency approved Reglan® tablets for the treatment of gastroesophageal reflux (GER), and the approved labeling included that indication in 1985. That labeling stated that treatment with the drug for longer than 12 weeks "has not been evaluated and cannot be recommended." In addition, the following three paragraphs describing tardive dyskinesia, a movement disorder, were added:

> Tardive Dyskinesia: Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with metoclopramide. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients are likely to develop the syndrome. Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase

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[1] The 1980 label identified movement disorders as a possible side effect. See Physicians' Desk Reference at 1566 (36th ed. 1982).

> with the duration of treatment and total cumulative dose.
>
> Less commonly, the syndrome can develop after relatively brief treatment periods at low doses; in these cases, symptoms appear more likely to be reversible.
>
> There is no known treatment for established cases of tardive dyskinesia although the syndrome may remit, partially or completely, within several weeks to months after metoclopramide is withdrawn. Metoclopramide itself, however, may suppress (or partially suppress) the signs of tardive dyskinesia, thereby masking the underlying disease process. The effect of this symptomatic suppression upon the long term course of the syndrome is unknown. Therefore, the use of metoclopramide for the symptomatic control of tardive dyskinesia is not recommended.[1]

In 2004, the labeling for metoclopramide was again revised. Although the section on tardive dyskinesia remained the same, the following sentence was added to the "Indications and Usage" section:

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[1] See Physician's Desk Reference at 1060 (39th ed. 1985); Physician's Desk Reference at 1635 (41st ed. 1987).

> The use of metoclopramide tablets is recommended for adults only. Therapy should not exceed 12 weeks in duration.[5]

The next change relating to tardive dyskinesia was made in March 2009, when FDA, based on "new safety information," and using the new labeling authority granted by FDAAA, issued a letter requiring that all holders of applications for brand metoclopramide products make changes to their respective labels regarding the tardive dyskinesia warnings, including the addition of a black box warning.[6] All ANDA holders for those products were required to adopt the new labeling requirements, but not until the brand labels were changed. *See* ANDA Labeling Revision Guidance at 4-5. The labeling changes requested by FDA in March 2009 were submitted in supplemental applications and approved by FDA on June 30, 2009.[7]

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[5] 2004 Reglan® Label, Indications and Usage at 6 *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/17854s047lbl.pdf (last visited Jan. 23, 2011).

[6] *See* Risk Evaluation and Mitigation Strategies (REMS) Letters to Sponsor/Applicants Requesting Label Changes, *available at* http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm148710.htm (last visited Jan. 23, 2011).

[7] *See* Letter from FDA to Maven Pharmaceuticals, LLC, June 30, 2009, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2009/017854s051,021793s001ltr.pdf (last visited Jan. 23, 2011).

There were only three differences between the 2004 and 2009 labels. First, the black box warning was added. Second, the last sentence of the warning contained a new statement that directly linked use beyond 12 weeks to a risk of tardive dyskinesia. Third, the last statement in the first paragraph of the warnings section added a statement about the prevalence of the disease – *i.e.*, that one published study reported a 20% prevalence level for patients treated for at least three months. In November 2010, however, FDA withdrew that sentence, substituting a statement that 20% of those using the drug do so for more than 12 weeks.[8]

Although no changes were made to the metoclopramide label between 2004 and 2009, FDA extensively reviewed information regarding the safety of metoclopramide during that period in connection with a new drug application submitted by Pozen Inc., for a combination product. During that review, both FDA and an advisory committee examined safety issues related to long-term metoclopramide use and tardive dyskinesia. For example, in a May 18, 2004 memo by Eric Bastings M.D., the Neurology Team Leader in the Center for Drug Evaluation and Research, Dr. Bastings acknowledged concerns regarding extrapyramidal adverse events known to be caused by metoclopramide, and cited medical literature noting that movement disorder specialists believed that to prevent persistent movement disorders, long-term use should be avoided. Dkt. Entry 78, *Mensing v.*

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[8] 2010 Reglan® Label, Warnings at 5, *available at*: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/017854s055lbl.pdf (last visited Jan. 23, 2011).

Wyeth, Inc., 07-cv-3919 (D. Minn.) (Exh. FF to Second Clark Affidavit at 6-8). On May 5, 2005, Mary Ross Southworth, Pharm.D., a Safety Evaluator in the Division of Drug Risk Evaluation in FDA's Center for Drug Evaluation and Research, also issued a memo concluding that data demonstrated that the occurrence of irreversible movement disorders is largely a risk associated with chronic use of metoclopramide. Dkt. Entry 78, *Mensing v. Wyeth, Inc.*, 07-cv-3919 (D. Minn.) (Exh. GG to Second Clark Affidavit at 3, 27).

FDA also conducted a study of the outpatient prescribing and drug-use patterns for metoclopramide as well as the duration of therapy for the drug. The study found that there had been a substantial increase in the number of prescriptions dispensed for patients using metoclopramide for a longer than recommended duration. Specifically, data showed that about 10% of the study population used metoclopramide for more than six months. Dkt. Entry 78, *Mensing v. Wyeth, Inc.*, 07-cv-3919 (D. Minn.) (Exh. HH to Second Clark Affidavit at 22).

B. Proceedings Below.

Petitioners manufacture metoclopramide, a generic form of Reglan®. According to the allegations of their complaints, respondents Gladys Mensing and Julie Demahy were each prescribed metoclopramide for several years, contrary to labeling stating that treatment should not exceed 12 weeks. Respondents

each developed tardive dyskinesia, which they attribute to long-term use of metoclopramide."

1. Mensing

Mensing filed suit in the federal court in Minnesota in 2007. Mensing's 203-paragraph First Amended Complaint, which also named as defendants the manufacturer of Reglan® (Wyeth, Inc.), and other manufacturers of metoclopramide, alleged numerous causes of action under Minnesota law. The court granted Actavis's motion to dismiss Mensing's complaint. According to the court, "a generic drug manufacturer cannot unilaterally change its label without prior FDA approval," and "it would be impossible for [the generic manufacturers] to abide by both state and federal laws." JA 382-83. The court held that this conflict would also stand as an obstacle to the accomplishment of the full purposes and objectives of Hatch-Waxman, a key purpose of which is to increase the availability of safe and effective, low-cost generic drugs and to relax the generic approval and labeling process. JA 383.

The court also rejected the argument that the generic defendants could have sought to strengthen their warnings through the prior approval supplement process. JA 383-84. Finally, the court recognized that generic drug manufacturers are not permitted to send "Dear Doctor" letters as a means of providing additional or different warnings. JA 384.

" Mensing was prescribed metoclopramide from 2001 to 2005 and Demahy was prescribed the drug from 2002 to 2007. JA 21-22, 434-35. Neither discontinued the use of metoclopramide after FDA added the warning against long-term use in 2004.

Again, the court concluded that enforcing a state law duty that would require generic drug manufacturers to send "Dear Doctor" letters would directly conflict with the statutory scheme. JA 384. Further, the court concluded that "speculation over what the FDA might have done if [the generic defendants] had requested such a letter would stand as an obstacle to the accomplishment and execution of the full purposes and objectives of the Act." JA 384.

The Eighth Circuit reversed in a decision that relied heavily on *Wyeth*. JA 400-21. The court discussed whether a generic manufacturer can change its label before the brand has made such a change, but then stated that "[i]n this case we need not decide whether generic manufacturers may unilaterally enhance a label warning" because "the generic defendants could have at least *proposed* a label change that the FDA could receive and impose uniformly on all metoclopramide manufacturers if approved." JA 409-10. The court also held that "the generic manufacturers could have suggested that the FDA send out a warning letter to health care professionals." JA 413.

2. Demahy

Demahy filed suit in state court in Louisiana, and, after the case was removed, the district court denied Actavis's motion to dismiss Demahy's complaint. JA 477-519. Following Actavis's interlocutory appeal, the Fifth Circuit affirmed. JA 520-63. While acknowledging that Hatch-Waxman required that Actavis's product have the same label as Reglan® at the time it was approved, the Fifth

Circuit held that if there were new safety information, Actavis could have changed its label after approval and that therefore Demahy's claims were not preempted. The court rejected Demahy's contention that Actavis could have communicated directly with physicians about the risks associated with prolonged use of metoclopramide without FDA approval, although it held that "generic manufacturers . . . [could] suggest that FDA send such letters on their behalf." JA 353.[3]

SUMMARY OF THE ARGUMENT

Respondents' state law failure-to-warn claims against Actavis run headlong into core federal conflict preemption principles. A classic conflict exists when compliance with state and federal law is impossible, as it is here. Actavis could not have unilaterally changed its warning label as respondents' state law claims would require, and simultaneously complied with federal law labeling requirements applicable to generic manufacturers. Respondents' claims are therefore preempted.

The FFDCA and FDA's implementing regulations require that a generic drug be a true copy of the brand drug in all significant respects, including labeling. 21 U.S.C. § 355(j)(2)(A). FDA's regulations also state that this identical labeling requirement applies to ANDAs. 21 C.F.R. § 314.94, which are defined to include the original application and any supplements thereto, including a supplement filed under the CBE regulation. 21

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[3] There are currently more than 1,000 metoclopramide cases pending in the federal and state courts.

C.F.R. § 314.3. Although FDA permits a brand manufacturer to make unilateral changes to its warning labels without prior approval by the Agency, 21 C.F.R. § 314.70(c)(6)(iii)(A), (C), generic manufacturers may use the CBE regulation only to parrot warning language that a brand manufacturer already has added to its label under that same regulation.

That generic manufacturers cannot use the CBE regulation to deviate from the brand label is entirely consistent with this Court's decision in *Wyeth*, a case involving a brand manufacturer to whom the generic labeling restrictions did not apply. In that case, this Court held that plaintiff's state law claims were not preempted because the brand manufacturer could have used the CBE regulation to make a unilateral change to its warning label. That option is foreclosed to generic manufacturers.

The other option available to brand manufacturers to warn healthcare professionals – a "Dear Doctor" letter – is similarly unavailable to generic manufacturers, since the FFDCA and the Agency's regulations treat such letters as labeling. The only state law claims alleged in respondents' complaints are respondents' failure-to-warn claims, and they are preempted.

The Fifth and Eighth Circuits, however, raised the specter of a hypothetical state law claim for failing to "take steps" to propose a label change to FDA. Respondents have not identified how such a theory could fit into the state failure-to-warn claims that they asserted in their complaints, nor have they

identified any law in either Minnesota or Louisiana supporting the viability of such a claim

At every juncture, from the gateway of preemption to respondents' ability to prove that Actavis failed to "take steps," to the essential element of causation, respondents would face roadblocks If respondents are arguing that generic manufacturers have the same duty to gather safety data and perform studies as the brand, that claim would be preempted as contrary to the underlying goals of Hatch-Waxman

In addition, respondents would fare no better in their efforts to prove the causation element of a "take steps" claim They would have the burden of proving not only that Actavis had new and significant safety information to share with FDA, but also that FDA would have agreed that a labeling change was appropriate, that it would have proceeded to ask the brand to change its label, and that the brand would have agreed Each link in this chain would be pure speculation

Respondents' cases should be dismissed

ARGUMENT

I. STATE LAW CLAIMS BASED ON THE GENERIC DRUG MANUFACTURER'S FAILURE TO CHANGE WARNINGS ON THE LABEL OF ITS GENERIC DRUG OR TO NOTIFY HEALTHCARE PROFESSIONALS OF NEW SAFETY INFORMATION ARE PREEMPTED.

A. Generic manufacturers may not unilaterally add safety information to the labels of their generic drugs.

The FFDCA and FDA's implementing regulations require a generic drug to have the same label as the brand. Under Hatch-Waxman:

> An abbreviated application shall contain . . . information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug.[1]

21 U.S.C. § 355(j)(2)(A). FDA's regulations also require that each ANDA contain "[a] statement that the applicant's proposed labeling . . . is the same as the labeling of the reference listed drug." 21 C.F.R.

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[1] The statute defines "listed drug" as a drug "which has been approved for safety and effectiveness under subsection [355](c)" which is the section applicable to approval of NDAs. 21 U.S.C. § 355(j)(7); *see also id.* at § 355(j)(2)(A)(i).

§ 314.94(a)(8)(iii).[2] The regulations further define "abbreviated application" as including all amendments and supplements to an application. 21 C.F.R. § 314.3(b).

That definition of "abbreviated application" is central to this case and was not even cited by the Fifth Circuit in *Demahy*. It declares that an "[a]bbreviated application means the application described under § 314.94 [the section that spells out the content of ANDAs] *including all amendments and supplements to the application*." 21 C.F.R. § 314.3(b) (emphasis added). The term "abbreviated application" includes abbreviated new drug applications. *Id.*

Thus, the same labeling requirement set out in 21 U.S.C. § 355(j)(2)(A)(v) and 21 C.F.R. § 314.94 applies to the original ANDA, and to amendments and supplements to that ANDA. Any change made in a supplement, pursuant to the CBE regulation or otherwise, is therefore subject to the same labeling requirement, *i.e.*, the labeling in the supplement must also mirror the brand label.

A generic drug manufacturer may invoke the CBE regulation, but only to conform the generic drug's label to a change already made by the brand. The FDA regulations unequivocally prohibit the generic manufacturer from adding a warning to its label if that addition would make the generic label

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[2] The statute and regulations permit certain differences in labeling that are not applicable here. See 21 U.S.C. § 355(j)(2)(A)(v); 21 C.F.R. § 314.94(a)(8)(iv).

different from the brand. In fact, FDA may "withdraw approval of [an] abbreviated new drug application . . . if the agency finds [t]hat the labeling . . . is no longer consistent with that for the [brand] drug." 21 C.F.R. § 314.150(b)(10).

When it issued the proposed rule implementing Hatch-Waxman, FDA stated that it "will not accept ANDAs for products with significant changes in labeling (such as new warnings or precautions) intended to address newly introduced safety or effectiveness problems not presented by the listed drug." Abbreviated New Drug Application Regulations, Proposed Rule, 54 Fed. Reg. 28872, 28884 (July 10, 1989).[3]

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[3] FDA's decision recognized the control that the brand manufacturers have over the proprietary scientific information that drives label changes. The generic manufacturers, by contrast, receive a small percentage of the total AERs and do not have the same access to the scientific safety history of any particular drug. As a result, the brand manufacturer, which is in a superior scientific position to most generics, is in the best position to analyze the safety data and to determine whether a label change is necessary. In addition, the effect of requiring generic manufacturers to maintain the same label as the brand is that the generic manufacturers also must have the same label as each other. For any given brand name drug, there can be multiple generic versions. There are, for example, six approved therapeutically equivalent versions for each strength of Reglan® tablets. *See* Reglan® Therapeutic Equivalents, http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Generics (last visited Jan. 23, 2010) (search for "Reglan," click on NDA No. 17854, then click on "therapeutic equivalents"). If each generic manufacturer for a particular brand name drug were able to make unilateral changes to its label, the result could be a variety of different warnings among the generic versions of a drug, not to mention the fact that all of those generic labels would deviate from the brand.

Two of the comments to the proposed regulation urged FDA to revise the proposal "to permit ANDA applicants to deviate from the labeling for the reference listed drug to add contraindications, warnings, precautions, adverse reactions, and other safety-related information." Abbreviated New Drug Application Regulations, Final Rule, 57 Fed. Reg. 17950, 17961 (April 28, 1992). FDA responded that it "disagree[d] with the comments." *Id.* According to the Agency, "the ANDA product's labeling must be the same as the listed drug product's labeling because the listed drug product is the basis for ANDA approval." *Id.* The Agency went on to explain that "[c]onsistent labeling will assure physicians, health professionals, and consumers that a generic drug is as safe and effective as its brand name counterpart." *Id.*

This consistent labeling requirement applies at all times. Thus, if the brand drug changes its labeling after a generic is on the market, the generic must revise its label. *See* ANDA Labeling Revision Guidance at 4; *see also* 21 C.F.R. §§ 314.3, 314.94(a)(8)(iv). In fact, even if FDA requires labeling changes for the brand, as it did when it revised the prescription drug label format, the generic must wait until the brand changes its label before making the changes. *See* Requirements on Content and Format of Labeling for Human Prescription Drugs and Biological Products, Final Rule, 71 Fed. Reg. 3922, 3928 (Jan. 24, 2006); *see also* Proposed Rule, 65 Fed. Reg. 81082, 81098 (Dec. 22, 2000). If a generic does not maintain the same

label as the brand. FDA can remove the generic from the market. 21 C.F.R. § 314.150(b)(10).

Under the FFDCA, the Agency has the authority to "promulgate regulations for the efficient enforcement" of the Act. 21 U.S.C. § 371(a). As explained above, the plain and only meaning of FDA's regulations is that at all times the labeling of generic drugs must be the same as the brand. There can be no question here that those regulations are consistent with the plain meaning, and that they are a permissible interpretation of the Act. *See Chevron, U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837, 842-44 (1984). In addition, the Agency's regulations preempt state failure-to-warn claims which would require a generic manufacturer to unilaterally change its label. *See Hillsborough County v. Automated Med. Labs.*, 471 U.S. 707, 713 (1985); *Fidelity Fed. Sav. & Loan v. de la Cuesta*, 458 U.S. 141, 153-54 (1982). If, however, there were any ambiguity in the Agency's regulations, which have the force of a law, then the Agency's consistent and longstanding interpretation of those regulations would be entitled to deference. *See Auer v. Robbins*, 519 U.S. 452, 462-63 (1997); *Thomas Jefferson Univ. v. Shalala*, 512 U.S. 504, 512 (1994).

In concluding that the generic manufacturer may change its label even though the brand has not, the Fifth Circuit read the CBE regulation as if it exists alone instead of as part of a larger regulatory scheme. FDA regulations must be read together and in a manner that allows a manufacturer to comply with all of the requirements. *See Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 631-

632 (1973). If the relevant regulations are read together, then they plainly require the labeling for an ANDA product to correspond to that for the brand reference drug.

The Fifth Circuit cited an FDA regulation, 21 C.F.R. § 314.97, which states that a generic drug applicant must comply with the CBE regulation, 21 C.F.R. § 314.70, to support its assertion that a generic manufacturer may unilaterally add warning information to its label. JA 545-46. The court, however, neglected to discuss the definition of "abbreviated application," 21 C.F.R. § 314.3, which, when read together with the requirement that an ANDA's labeling be the same as the labeling on the brand reference product at all times, 21 C.F.R. § 314.94(a)(8)(iii), prohibits the filing of a supplement under the CBE regulation with a warning or other provision that differs from the brand. There is no inconsistency between 21 C.F.R. § 314.97 and the same labeling regulations (sections 314.3 and 314.94(a)(8)(iii)), and the only way to read the provisions in harmony is to read the same labeling regulations as a limitation on section 314.97. While section 314.97 requires a generic drug manufacturer to use the CBE regulation to change its label to match a change in the brand label, the Fifth Circuit was wrong in concluding that it provides any authority for the generic manufacturer to unilaterally change its label.

Petitioner's position on the unavailability of the CBE regulation to make unilateral label changes is unequivocally supported by FDA. Brief for the United States as Amicus Curiae, filed in Nos. 09-993

and 09-1039 on November 2, 2010 (US Cert. Br.). The United States declares that "[t]he holder of an approved ANDA is not free to change its approved labeling at will." US Cert. Br. 12. In fact, the United States directs the Court's attention to the same regulations, guidance documents and preamble language cited above and notes that FDA has consistently taken the position that an ANDA holder may not unilaterally change its approved labeling. U.S. Cert. Br. 13-14.

B. Generic manufacturers may not unilaterally send "Dear Healthcare Professional" letters that contain warnings about their drugs that are different from those of the branded drug.

"Dear Healthcare Professional" (DHCP) letters may be sent by manufacturers to the healthcare professionals who prescribe their drugs. These letters may address many topics, including warnings and safety-related information. *See* FDA, Center for Drug Evaluation & Research, NDAs: "Dear Health Care Professional" Letters, *Manual of Policies & Procedures* 6020.10 (July 2, 2003); *see also* 21 C.F.R. § 200.5 (containing formatting and content restrictions for DHCP letters). The type of DHCP letters on which respondents' failure-to-warn claims are grounded would have provided healthcare professionals with different warnings for petitioners' products. The Eighth Circuit, the Fifth Circuit, and the Solicitor General correctly concluded that petitioners could not have lawfully made a unilateral

change to their warning label through a DHCP letter. JA 413, 553; US Cert. Br. 17-18.

The potential conflict caused by DHCP letters of this nature is twofold. First, labeling is defined broadly under the FFDCA and includes such letters. 21 U.S.C. § 321(m); 21 C.F.R. § 202.1(l)(2) ("[b]rochures, booklets, mailing pieces . . . letters . . . containing drug information supplied by the manufacturer are . . . labeling"). If a generic manufacturer acts unilaterally to change its label through a DHCP letter containing a new warning, it will have violated the statutory and regulatory requirements discussed in Section I.A above that mandate its labeling mirror that of the brand.

Second, FDA may withdraw approval of an ANDA if "the labeling of the drug, based on a fair evaluation of all material facts, is false or misleading in any particular." 21 C.F.R. §§ 314.150(b)(3), (10); *see also* 21 U.S.C. § 321(n) (defining drug as "misbranded" if its labeling is false or misleading). If petitioner had sent a DCHP letter changing the warnings for its product, the letter would have rendered its labeling misleading. As the United States explained, "an ANDA holder's letter warning about risks seemingly unique to its product could mislead consumers and providers into believing that the generic drug and RLD were not therapeutic equivalents." US Cert. Br. 17-18.

* * *

In *Wyeth*, this Court held that "it is not impossible for Wyeth to comply with its state and

federal law obligations." 129 S. Ct. at 1204. Those obligations could be reconciled because "[t]he CBE regulation permitted Wyeth to unilaterally strengthen its warning." *Id.* at 1199. But generic manufacturers do *not* have the ability to unilaterally change their labeling, either through a CBE supplement or a DHCP letter. It is legally impossible for them to satisfy a jury-imposed duty to add warnings that differ from the warnings on the brand label.

II. RESPONDENTS AND THE LOWER COURTS HAVE NOT IDENTIFIED A STATE LAW CLAIM THAT PREVENTS DISMISSAL, AND ANY SUCH CLAIM WOULD BE BASED ON SPECULATION.

As demonstrated above, respondents' state law claims that Actavis should have strengthened the labeling of its metoclopramide product or directly warned healthcare professionals are preempted. The *Mensing* court's conclusion that it did not need to decide whether a generic manufacturer could unilaterally change its label because, "a generic manufacturer must take steps to warn its customers when it learns it may be marketing an unsafe drug." JA 410, does not support a different result.[11] Nor

[11] In fashioning a speculative "take steps" claim, the Eighth Circuit expressed a concern that otherwise "injured parties like Mensing" would be left with "no legal remedy." JA 418. This concern was misplaced. Any lack of legal remedy would not be due to the success of petitioner's preemption arguments, but to a strategic decision by respondents. Respondents could have alleged state law claims against their physicians who prescribed metoclopramide beyond the treatment period permitted by the

does either court's conclusion that Actavis could have asked FDA to distribute a DHCP letter. None of the courts below identified any basis in Minnesota or Louisiana law for such a claim. In their complaints, neither plaintiff identified any state cause of action that could be the basis of a "take steps" claim.

If the Eighth Circuit is suggesting that plaintiffs could hold the generic companies liable for their alleged injuries based on the generic companies' failure to perform the kind of pharmacological due diligence and other duties required of brand manufacturers, their claims would be preempted. As the Solicitor General has explained, "imposing on a generic manufacturer a state law duty not to market its product without developing for itself knowledge as comprehensive as FDA's or the NDA holder's could pose preemption questions." U.S. Cert. Br. 22.

Although the Eighth Circuit concluded that federal regulations required a generic company to "take steps to warn its customers when it learns that it may be marketing an unsafe drug" by notifying FDA, neither it nor the respondents have explained how such a federal obligation could fit into the state failure-to-warn claims that plaintiffs asserted in their complaints nor have they identified any law in either Minnesota or Louisiana indicating such a claim would be viable.[5]

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label but they elected not to do so, instead pursuing only claims against the generic manufacturers.

[5] Respondents did state in their briefs below that Actavis could have proposed a label change to FDA through the prior

Respondents' failure to plead a claim based on a generic manufacturer's alleged failure to "take steps" to request a label change or otherwise present safety information to the FDA is understandable for another reason. Even if not preempted, and even if theoretically permitted under state law, such a claim has no path for establishing the essential element of causation.

Any claim that might be asserted by Mensing or Demahy based on an alleged duty to "propose" a labeling change to FDA, "suggest" that FDA issue a "Dear Doctor" letter, or "take steps" to warn by providing FDA information, would face daunting challenges. Every tort claim requires proof of causation (see, *e.g.*, Restatement (Third) of Torts: Liability for Physical and Emotional Harm §§ 18 comment *c*, 26, 28(a)), and any attempt by Mensing to assert the Eighth Circuit's proposed "take steps" claim would thus require her to prove that Actavis's failure to provide additional information to FDA "caused" her injury.

This Court's discussion of causation in *Wyeth* is not to the contrary. The issue in *Wyeth* was proof of preemption as a legal defense to liability, not proof of causation as a necessary element of a prima facie case of tort liability. Since in *Wyeth* the defendant would be arguing that it would be "impossible for it to comply with both federal and state requirements,"

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approval supplement process. See Mensing Opp. to Mot. to Dismiss at 32 (District Court Dkt. Entry 71); Demahy Opp. to Mot. to Dismiss at 8-9 (District Court Dkt. Entry 29); Mensing Reply Br. at 11 (Eighth Circuit filed May 18, 2009). These arguments were not tied to a state law claim.

the Court held that such a defense should not be accepted "absent clear evidence that the FDA would not have approved a change" to the drug's label that had already been made by the manufacturer. 129 S.Ct. at 1198. Because the issue was whether FDA would have made a specific decision to veto a label change that satisfied state law obligations, the burden of proof was on the defendant.

Theoretical "take steps" liability presents an entirely different scenario. If the state law duty is to propose a label change or otherwise "take steps," liability for compensation involves proof that fulfillment of the duty would have prevented the injury. State law, not federal law, imposes the burden of demonstrating what FDA would have done on the plaintiff. Indeed, for a claim that arose before September 2007 (the time period applicable to both *Mensing* and *Demahy*), proving a causal link between the act or omission of a generic drug manufacturer and an injury that could have been avoided by a warning involves both proving that FDA would have been persuaded that additional warnings were appropriate and – since FDA could not at that time order a label change on its own authority – persuading the brand manufacturer (who controlled the label) to change it.

To meet that burden, Mensing would have had to prove not only that Actavis had new information that it did not present to FDA (not alleged here), but also that FDA would have urged the brand manufacturer to change its label based on the "new" information – a matter of pure speculation. Expert testimony about what FDA would have done if asked

to change the label on a drug or to warn healthcare professionals about a drug is inherently speculative and cannot meet the standards for admissibility and reliability under Federal Rule of Evidence 702 and *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579 (1993). Indeed, courts have generally excluded expert testimony about what actions FDA might have taken with respect to regulation of its products.[illegible] Thus, not only is it likely that the plaintiffs in the instant cases would have difficulty proving "take steps" claims, had they been alleged, any plaintiff is likely to be barred from asserting a claim that a generic manufacturer should have requested FDA

[illegible] For example, in *Bartlett v. Mutual Pharmaceutical Co.*, No. 08-cv-358, 2010 WL 2889114, at *14 (D.N.H. July 22, 2010), a product liability case where the plaintiff had argued that Mutual, a generic drug company, should have unilaterally changed its label, the court excluded "speculation as to what FDA might have done in hypothetical circumstances" (citation omitted). Numerous other trial courts have excluded testimony about whether FDA would have taken a particular action as speculative. *In re Trasylol Prods. Liab. Litig. MDL 1928*, 2010 WL 4259332, at *8-12 (S.D. Fla. Oct. 21, 2010) (excluding as "speculation" testimony regarding what FDA "would have done in hypothetical circumstances"); *In re Bayol Prods. Litig.*, 532 F. Supp. 2d 1029, 1053-54 (D. Minn. 2007) (excluding as "speculation" testimony that particular statements by a drug company "likely played a role in the Agency's allowing the clinical investigation program to go forward"); *Twin Cities Bakery Workers Health & Welfare Fund v. Biovail Corp.*, 2005 WL 3675999, at *3-5 (D.D.C. Mar. 31, 2005) (excluding testimony as "too speculative" that FDA would have approved a drug but for misuse of a patent); *aff'd*, *Meijer, Inc. v. Biovail Corp.*, 533 F.3d 857, 863 (D.C. Cir. 2008); *In re Rezulin Prods. Liab. Litig.*, 309 F. Supp. 2d 531, 550 n.62 (S.D.N.Y. 2004) (excluding expert testimony that amounted to "speculation as to what FDA might have done in hypothetical circumstances").

take regulatory action on the grounds that evidence essential to such a claim is pure speculation.[7]

Finally, even if a path could be identified for proving causation in a "take steps" claim, the regulatory record for metoclopramide highlights the weakness of any such claim. That record demonstrates that the FDA was fully apprised of all the issues related to metoclopramide and the risks of tardive dyskinesia. FDA not only oversaw the various metoclopramide labeling changes through 2004, but in 2004 and 2005 FDA closely scrutinized the safety of metoclopramide and it could have requested additional labeling changes if it had concluded that those changes were warranted. FDA's active consideration of an extensive record concerning the safety of metoclopramide demonstrates that for this product FDA was in a position to take action if the Agency had believed that such action was necessary.

The record is also devoid of evidence that Actavis had any information about the use of metoclopramide and the risk of tardive dyskinesia that was unknown to FDA. In 2004 and 2005, FDA reviewed a new drug application (NDA 21-645) submitted by Pozen Inc. for a combination metoclopramide product. During the review of this application, both FDA and an advisory committee thoroughly examined safety issues related to long-term metoclopramide use and tardive dyskinesia. FDA looked at all AERs as well as published articles

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[7] The same analysis would apply to an argument that Actavis should have asked FDA to direct generic manufacturers to send out DHCP letters.

that studied the safety of metoclopramide. The Agency conducted an internal review and found that the data demonstrated that the occurrence of irreversible movement disorders is largely a risk associated with chronic use of metoclopramide and that the cases from the AER database correlated well with what had been reported in the literature. See pp. 11-12, *supra*.

In preparation for an advisory committee review of the Pozen application, FDA also conducted a review of the outpatient prescribing and drug use patterns for metoclopramide in the United States as well as the duration of therapy for the drug. That study found that there had been a substantial increase in the number of prescriptions dispensed for metoclopramide along with a longer than recommended duration of use. See p. 12, *supra*.

Despite FDA's thorough review of issues related to the use of metoclopramide and tardive dyskinesia, including its review of metoclopramide AERs related to movement disorders, and despite its understanding that metoclopramide was being used for periods of time beyond the labeled recommendations, FDA did not require manufacturers to revisit metoclopramide labeling until 2009, after it had gained new authority to order a change in drug labels, which occurred after both Mensing and Demahy had stopped using the drug. There is no information that Actavis could have added to the extensive information that FDA reviewed during this period of time and thus no steps that Actavis could have taken that would have changed FDA's course of action.

Simply put, respondents did not allege a take steps claim; neither they nor the courts below identified such a claim in state law; and, in any event, respondents could not prove such a claim.

CONCLUSION

The decisions below should be reversed and remanded with directions to dismiss all claims.

Respectfully submitted.

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January 24, 2011

PETITIONER'S BRIEF

Nos. 09-993 VIDE 09-1039, 09-1501

Supreme Court, U.S.
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JAN 24 2011
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In The Supreme Court of the United States

PLIVA, INC., *ET AL.*, 09-993 *vide* 09-1039, *Petitioners*,

v.

GLADYS MENSING, *Respondent*.

ACTAVIS ELIZABETH LLC, 09-1039 *vide* 09-993, *Petitioner*,

v.

GLADYS MENSING, *Respondent*.

ACTAVIS INC., 09-1501, *Petitioner*,

v.

JULIE DEMAHY, *Respondent*.

On Writs of Certiorari to the U.S. Courts of Appeals for the Fifth and Eighth Circuits

BRIEF OF PETITIONERS PLIVA, INC.; TEVA PHARMS. USA, INC.; AND UDL LABS, INC.

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QUESTION PRESENTED

The Drug Price Competition and Patent Term Restoration Act (the "Hatch-Waxman Act") allows for the approval of low-cost generic drug products through an abbreviated process that hinges on the requirement that generic drug products—and their warnings—must in all material respects be "the same as" their FDA-approved brand-name equivalents.

Does the Hatch-Waxman Act preempt state-law failure-to-warn claims against the manufacturer of a generic drug whose warnings were, as the Hatch-Waxman Act and the FDA's implementing regulations expressly require, "the same as" those the FDA approved for the product's brand-name equivalent?

LIST OF PARTIES

Pursuant to this Court's Rule 24.1(b), the parties to these cases in their respective appellate courts were:

Nos. 09-993 and 09-1039 (Eighth Circuit)

A. Defendants-Appellees

PLIVA, Inc.
Teva Pharmaceuticals USA, Inc.
UDL Laboratories, Inc.
Actavis Elizabeth LLC
Wyeth, LLC

B. Plaintiff-Appellant

Gladys Mensing

No. 09-1501 (Fifth Circuit)

A. Defendant-Appellee

Actavis Inc.

B. Plaintiff-Appellant

Julie Demahy

CORPORATE DISCLOSURE STATEMENT

Pursuant to this Court's Rules 24.1(b) and 29.6:

Petitioner PLIVA, Inc. is an indirect wholly owned subsidiary of Teva Pharmaceutical Industries Ltd. through the following parent companies: Barr Laboratories, Inc., which in turn is directly owned by Barr Pharmaceuticals, LLC, which in turn is directly owned by Teva Pharmaceuticals USA, Inc., which in turn is directly owned by (i) Orvet UK Unlimited (Majority Shareholder), which in turn is directly owned by Teva Pharmaceuticals Europe B.V., which in turn is directly owned by Teva Pharmaceutical Industries Ltd.; and (ii) Teva Pharmaceutical Holdings Coöperatieve U.A. (Minority Shareholder), which in turn is directly owned by IVAX LLC, a direct subsidiary of Teva Pharmaceuticals USA, Inc. Teva Pharmaceutical Industries Ltd. is the only publicly traded direct or indirect parent company of PLIVA, and no other publicly traded company owns more than 10% of its stock.

Petitioner Teva Pharmaceuticals USA, Inc. ("TUSA") is an indirect wholly owned subsidiary of Teva Pharmaceutical Industries Ltd. through the following parent companies: (i) Orvet UK Unlimited (Majority Shareholder), which in turn is directly owned by Teva Pharmaceuticals Europe B.V., which in turn is directly owned by Teva Pharmaceutical Industries Ltd.; and (ii) Teva Pharmaceutical Holdings Coöperatieve U.A. (Minority Shareholder), which in turn is directly owned by IVAX LLC, a direct subsidiary of TUSA. Teva Pharmaceutical Industries Ltd. is the only publicly traded direct or indirect parent company of TUSA, and no other

publicly traded company owns more than 10% of its stock.

Petitioner UDL Laboratories, Inc. is a wholly owned subsidiary of Mylan Inc., which is the only publicly traded company that directly or indirectly owns 10% or more of UDL Laboratories, Inc.

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INTRODUCTION

In 1984, the Hatch-Waxman Act revolutionized the pharmaceutical market by giving rise to the modern generic drug industry. Until that point, virtually no modern drugs had generic equivalents. That was so because federal law required that *all* drugs—branded and generic alike—undergo independent clinical testing to prove their safety and efficacy. The significant costs required to do so effectively eliminated any incentive to duplicate previously approved drugs, and consumers continued to pay sky-high prices for basic medications long after the patents protecting those drugs had expired.

Hatch-Waxman took direct aim at that regime by drawing sharp distinctions between brand-name drugs and their generic equivalents. While branded products remained subject to extensive clinical-testing requirements, the new law allowed generic manufacturers to rely on the brand manufacturer's prior studies to prove the safety and efficacy of their own duplicate products. That radical departure was based on a simple premise: Where two drug products are in all material respects *the same*, they will share *the same* safety and efficacy profile.

Because the basis for Hatch-Waxman's abbreviated approval process is thus that uniformity will ensure the safety and efficacy of generic drugs, the entire regulatory scheme hinges on the requirement that there be no material differences between branded and generic drugs. Accordingly, the statute and FDA's implementing regulations require each generic drug to be "the same as" its branded equivalent in all material respects—including the chemical composition of its active

ingredient, its dosage form, its strength, its route of administration, the rate and extent to which it delivers the active ingredient to patients, and its labeling (including its warnings, whether affixed to the product or disseminated through other means). Any other approach would undercut the essential premise that allows for abbreviated generic approvals, and raise significant doubts about the equivalence of branded and generic medications by wrongly suggesting that there is a qualitative difference between products that by law and in fact are "the same."

Hatch-Waxman's streamlined procedures for approving generic drugs and its singular focus on "sameness" have been remarkably successful in achieving Congress's goal: "'to get generic drugs into the hands of patients at reasonable prices—fast.'" *Andrx Pharms., Inc. v. Biovail Corp. Int'l*, 256 F.3d 799, 809 (D.C. Cir. 2001) (quoting *In re Barr Labs., Inc.*, 930 F.2d 72, 76 (D.C. Cir. 1991)). Today, some 200 companies market generic drugs in the United States, and a recent study by IMS Health concluded that the widespread availability of generic drugs saved $824 billion between 2000 and 2009. *See* Generic Pharmaceutical Association, *Savings Achieved Through The Use Of Generic Pharmaceuticals, 2000-2009* at 1 (July 2010).[1]

Despite the crucial role generic drugs play in controlling healthcare costs, the decisions in these

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[1] *Available at* http://www.gphaonline.org/about-gpha/about-generics/case/generics-providing-savings-americans (last visited January 23, 2011).

cases now threaten to upend the Hatch-Waxman framework and jeopardize FDA's administration of this carefully calibrated regulatory regime. For its part, the Fifth Circuit's decision in *Demahy* held that a generic drug must be the same as its branded equivalent *only* on the date FDA first approves the generic product. *Demahy v. Actavis, Inc.*, 593 F.3d 428, 436 (5th Cir. 2010), JA534-35. After that time, *Demahy* held, the statute does not prevent generic products from deviating—and generic companies thus can be subjected to state-law liability if they fail unilaterally to depart from the branded product warnings federal law obligated them to replicate as a condition of approval.

That approach is anathema to the federal scheme. At the threshold, it renders the sameness requirements for generic product labeling a dead letter by freeing generic manufacturers to use whatever warnings they want despite the law's repeated demands that they replicate the branded product's warnings to obtain approval. In practice, it means that every generic version of a branded drug could bear its own unique warnings, so that potentially dozens of products that purport to have *the same* safety profile will offer users a patchwork quilt of *different* safety warnings. And taken to its logical conclusion, the Fifth Circuit's interpretation would allow generic products to deviate from their branded equivalents *in every respect* following FDA approval: As *Demahy* construed the law's key terms, *none* of the statutory sameness requirements would apply after FDA first approves a generic drug. Suffice it to say, there is no basis in law or logic for that approach—as FDA consistently has explained for almost three decades.

For its part, the Eighth Circuit's *Mensing* decision at least acknowledged that "generic labels must be substantively identical to the name-brand label even after they enter the market," and thus that generic manufacturers may not unilaterally deviate from the branded product warnings. *Mensing v. Wyeth, Inc.*, 588 F.3d 603, 608 (8th Cir. 2009), JA409. *Mensing* nonetheless strained to salvage state-law claims against generic companies by declaring that petitioners "could have at least *proposed* a label change that the FDA *could* receive and impose uniformly on all metoclopramide manufacturers *if approved*." JA410 (first emphasis in original).

By design, however, the statutory and regulatory regime does not impose the kind of postmarketing surveillance requirements on generic companies that would enable them to develop and adequately propose such changes. And in any event, this Court's precedents squarely foreclose hypothetical *state-law* claims that hinge on *federal regulatory submissions*. The States are powerless to interfere in the "inherently federal" business of federal agencies, *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 347 (2000), and this Court long ago made clear that federal law preempts state-law claims that necessarily require speculation about how a federal agency would have exercised its authority in hypothetical cases, *Arkansas La. Gas Co. v. Hall* ["*Arkla*"], 453 U.S. 571, 581-82 (1981).

Indeed, as the government consistently has explained, such claims would impose unprecedented and impermissible burdens on FDA's administration of the regulatory scheme. *See, e.g.*, Br. for the United States as *Amicus Curiae* Supporting Petitioners at 7-

8, *Warner-Lambert Co. v. Kent*, 552 U.S. 440 (2008) (No. 06-1498) [the "*Warner-Lambert* Federal Br."], 2007 WL 4218889 ("Speculation by fact-finders about what FDA would have done in hypothetical circumstances invades the province of the agency. Moreover, a legal standard that turned on such speculation would inevitably lead parties to request burdensome and intrusive discovery from FDA concerning its approval of a drug, and thereby divert the agency from its core public health mission.").

The *Mensing* court was undeterred. It ultimately concluded that FDA-approved generic drugs could simply be taken off the market to avoid state tort liability: "The generic defendants were not compelled to market metoclopramide. If they realized their label was insufficient but did not believe they could even propose a label change, they could have simply stopped selling the product." JA416. Without belaboring the point, it is hard to imagine a result more at odds with the federal scheme. Hatch-Waxman's whole aim, after all, was to make generic copies of approved brand-name drugs widely available to the public and thereby lower healthcare costs. A state-law duty that effectively compels the withdrawal of generic drugs which fully comply with the express mandates of federal law runs directly counter to the federal regime, in clear violation of the Supremacy Clause.

The judgments should be reversed.

OPINIONS BELOW

The Eighth Circuit's decision in Nos. 09-993 and 09-1039 is reported at 588 F.3d 603 (8th Cir. 2009) and reprinted in the Joint Appendix ("JA") at JA400-421. The district court's principal decision regarding

the issues presented here is reported at 562 F. Supp. 2d 1056 (D. Minn. 2008). That decision and an unreported companion opinion are reprinted at JA364-99.

The Fifth Circuit's decision in No. 09-1501 is reported at 593 F.3d 428 (5th Cir. 2010) and reprinted at JA520-63. The district court's decision is reported at 586 F. Supp. 2d 642 (E.D. La. 2008) and reprinted at JA477-519.

JURISDICTION

The Eighth Circuit rendered its decision in Nos. 09-993 and 09-1039 on November 27, 2009, and the petitions were timely filed on February 19 and 25, 2010, respectively. The Fifth Circuit rendered its decision in No. 09-1501 on January 8, 2010, and the petition in that case was timely filed on June 7, 2010 (following an April 5 order extending the deadline). 28 U.S.C. § 1254 confers jurisdiction over each petition.

PERTINENT CONSTITUTIONAL, STATUTORY, AND REGULATORY PROVISIONS

The pertinent legal provisions are set forth in the Appendices to the petitions.

STATEMENT OF THE CASE

A. Statutory and Regulatory Background

1. The Original Statutory Scheme

The federal Food, Drug, and Cosmetic Act ("FDCA") governs the approval of pharmaceuticals in the United States. Until recently, its provisions applied equally to all drugs—branded and generic alike. Under the FDCA's 1962 amendments, *every* manufacturer of a post-1962 drug was required to

perform its own clinical studies to prove the product's safety and effectiveness. *Abbreviated New Drug Application Regulations—Final Rule*, 57 Fed. Reg. 17950, 17961 (Apr. 28, 1992), Pet. App. 96a.[2] That meant that even after the patents protecting branded drugs expired, no copy could be approved until its manufacturer replicated the brand company's clinical studies.

The 1962 regime had two consequences. *First*, the brand manufacturer benefited from a *de facto* extension of its patent monopoly. The patent laws at that time prevented generic companies from beginning clinical studies until patent expiry, and those studies—once initiated—took years to complete. *See, e.g.*, Laura J. Robinson, *Analysis of Recent Proposals to Reconfigure Hatch-Waxman*, 11 J. INTELL. PROP. L. 47, 52 (2003). As a result, branded companies often could maintain high prices long after patent expiry theoretically opened the door to competition. *Second*, the high costs of conducting independent clinical studies were reflected in generic prices—meaning that even after competition began, the price of *all* drugs remained considerable.

Not surprisingly, FDA approved few duplicate drugs under that regime. Except for outdated pre-1962 products that FDA allowed applicants to copy under its so-called "DESI" regulations,[3] and a few

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[2] Citations to the Pet. App. refer to the Appendix accompanying the Petition in No. 09-993.

[3] Under this process, FDA contracted with outside organizations to evaluate the safety and efficacy of pre-1962 drugs. The Agency then "required [generic] applicants to

post-1962 blockbuster drugs that FDA allowed applicants to duplicate through a controversial pathway called a "paper NDA,"[4] it was not cost-effective to make generic drugs. In 1984, generics filled less than 19 percent of all prescriptions, Richard G. Frank, *The Ongoing Regulation of Generic Drugs*, 357 NEW ENG. J. MED. 1993 (2007), and hundreds of branded drugs had no generic equivalent. Federal Trade Commission, *Generic Drug Entry Prior to Patent Expiration: An FTC Study* 4 (July 2002), *available at* http://www.ftc.gov/os/2002/07/genericdrugstudy.pdf (visited January 23, 2011).

2. The Hatch-Waxman Act

By the early 1980s, Congress recognized that millions of Americans were unable to afford both the basic necessities of life and essential medications. Congress also recognized that state and federal authorities were wasting billions of dollars each year on pricey branded drugs. *See* New Drug Application:

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submit information that showed the applicant's ability to manufacture a product of acceptable quality whose safety and effectiveness were equivalent to the drug product whose safety and effectiveness had been established." 57 Fed. Reg. at 17950, Pet. App. 96a-98a.

[4] *See* 57 Fed. Reg. at 17951, Pet. App. 99a ("This policy permitted FDA to approve NDA's for post-1962 drug products [based on] safety and effectiveness information derived primarily from published reports based on well-controlled studies. This meant that manufacturers did not have to conduct their own tests, but adequate literature [needed to support approval] was available for only a fraction of the post-1962 drugs.").

Hearings on H.R. 3605, Subcomm. on Health and the Env't, House Comm. on Energy & Commerce, 98th Cong., 1st Sess. (July 25, 1983) ["Subcomm. Hearings"], Pet. App. 114a-121a; P.L. 98-417, Drug Price Competition & Patent Term Restoration Act, H.R. Rep. No. 857(I), 98th Cong., 2d Sess. (June 21, 1984), *reprinted in* 1984 U.S.C.C.A.N. 2647, Pet. App. 122a-135a; Drug Price Competition & Patent Term Restoration Act of 1984, Comm. Notes, 130 Cong. Rec. 24416, H.R. 3605 (Sept. 6, 1984), Pet. App. 136a-146a.

To remedy those problems and thereby "get generic drugs into the hands of patients at reasonable prices—fast," Republican Senator Orrin Hatch and Democratic Representative Henry Waxman joined forces to create an abbreviated pathway for generic approvals. *Andrx*, 256 F.3d at 809 (quotation omitted); *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1568 (Fed. Cir. 1997) ("[T]he purposes of the legislation are 'to make available more low cost generic drugs,'" and "'provide regulatory relief, increase competition, economy in government, and best of all, [allow] the American people [to] save money, and yet receive the best medicine that pharmaceutical science can provide.'") (quoting *inter alia* Stmnt. On Signing S. 1538 Into Law, 20 Weekly Comp. Pres. Doc. 1359, 1360 (Sept. 24, 1984)).

The resulting Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1598 (Sept. 24, 1984)—now known as the "Hatch-Waxman Act"—for the first time drew sharp statutory distinctions between generic and branded drugs.

a. Approval Requirements For Brand-Name Drugs

Hatch-Waxman left brand manufacturers bound by the 1962 Act's requirements. Before seeking approval, they must obtain FDA permission to conduct clinical trials designed to establish the drug's safety and efficacy for treating a specific condition or disease. 21 U.S.C. § 355(i); 21 C.F.R. § 312.20. Once it receives consent and conducts its studies, the branded company must file a New Drug Application ("NDA") that includes "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use." 21 U.S.C. § 355(b)(1)(A).

The safety and efficacy of a new drug is tied to the conditions under which it is intended for use. FDA thus engages in a substantive review of the product's proposed labeling before approving an NDA. *See* 21 U.S.C. § 355(b)(1)(F); *see also New Drug and Antibiotic Regulation—Final Rule*, 50 Fed. Reg. 7452, 7470 (Feb. 22, 1985) ("Drug labeling serves as the standard under which FDA determines whether a [new drug] product is safe and effective.").

FDA's regulations delineate both the content and format of the labeling required for branded drugs. 21 C.F.R. §§ 201.56-201.57 (post-2001 drugs); *id.* § 201.80 (pre-2001 drugs). The regulations require drug labeling to include "a summary of the essential scientific information needed for the [product's] safe and effective use," *id.* § 201.56(a), and dozens of categories of information relating to the drug. *Id.* §§ 201.57, 201.80.

b. Approval Requirements For Generic Drugs

In contrast to branded applicants, generic applicants no longer need to submit a full NDA based on independent clinical trials. Instead, they are required to submit an Abbreviated New Drug Application (or "ANDA") showing that the generic product is identical in all material respects to a previously approved NDA product (called the "listed drug" or "reference listed drug"). 21 U.S.C. § 355(j)(2)(A). Accordingly, each proposed generic drug must present "the same" dosage form, strength, and route of administration of "the same" active ingredient in a formulation that is "bioequivalent"[5] to an approved brand-name drug, and thus naturally must bear "the same" warnings as the approved drug. *Id.* § 355(j)(2)(A)(i)-(v).

If the ANDA meets these criteria, its sponsor need not conduct its own clinical studies; instead, FDA relies upon the brand manufacturer's studies to validate the generic product's safety and efficacy. *Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060, 1063 (D.C. Cir. 1998). Indeed, FDA may *not* require an ANDA applicant to conduct its own clinical trials. *Id.* § 355(j)(2)(A). That makes sense. If a proposed generic drug is in all material respects "the same" as one FDA already approved, it will have "the same"

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[5] Generally speaking, two drugs are considered "bioequivalent" if there is "[no] significant difference in the rate and extent to which the active ingredient ... becomes available at the site of drug action when administered at the same molar dose under similar conditions." 21 C.F.R. § 320.1(e).

safety and efficacy profile. Repeating placebo-controlled clinical trials in which ill patients are deprived of essential medication thus would be both "unnecessary" and "unethical." Pet. App. 124a ("FDA considers such retesting to be unnecessary and wasteful because the drug has already been determined to be safe and effective. Moreover, such retesting is unethical because it requires that some sick patients take placebos and be denied treatment known to be effective.").

Because ANDA products are by definition "the same as" their branded equivalents, the statute and FDA regulations expressly require generic product warnings to be "the same as" those on the referenced brand-name drug. Each ANDA therefore must "show that the labeling proposed for the new drug is *the same as* the labeling approved for the listed drug," 21 U.S.C. § 355(j)(2)(A)(v) (emphasis added), and FDA must deny approval if "the application is insufficient to show that the labeling proposed for the drug is *the same as* the labeling approved for the listed drug." *Id.* § 355(j)(4)(G) (emphasis added). FDA regulations reiterate both requirements, *see* 21 C.F.R. § 314.94(a)(8); *id.* § 314.127(a)(7), and help implement them by requiring each ANDA to include a "side-by-side comparison of the proposed labeling [and] the approved labeling for the [brand-name] drug." *Id.* § 314.94(a)(8)(iv).

Of course, certain labeling differences are unavoidable. Petitioners' generic versions of Wyeth's Reglan® cannot, for instance, falsely represent that they too are manufactured by Wyeth. *See* 21 U.S.C. § 331(b); *id.* § 321(n). Hatch-Waxman therefore authorizes labeling variances where "the [generic]

drug and the [brand-name] drug are produced or distributed by different manufacturers." 21 U.S.C. § 355(j)(2)(A)(v). FDA has interpreted that language to permit differences

> in expiration date, formulation, bio-availability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity.

21 C.F.R. § 314.94(a)(8)(iv). The regulation pointedly does *not* authorize divergent product warnings.

That is no accident. FDA received dozens of comments when it proposed the regulation, including two submissions proposing that it "be revised to permit ANDA applicants to deviate from the labeling for the [branded] drug *to add contraindications, warnings, precautions, adverse reactions, and other safety-related information.*" 57 Fed. Reg. at 17961, Pet. App. 108a (emphasis added). FDA rejected the proposal:

> FDA disagrees with the comments. Except for labeling differences due to exclusivity or a patent and differences under section 505(j)(2)(v) of the act, *the ANDA product's labeling must be the same as the listed drug product's labeling because the listed drug product is the basis for ANDA approval.* Consistent labeling will assure physicians, health professionals, and consumers that a generic drug is as safe and effective as its brand-name counterpart.

Id., Pet. App. 109a (emphasis added; citing 21 U.S.C. § 355(j)(2)(A)(v)); *see also id.* at 17953, Pet. App. 104a ("As for accepting ANDA's with additional warnings or precautions ... the act requires that the applicant's proposed labeling be the same as that of the [branded] drug.") (citing 21 U.S.C. §§ 355(j)(2)(A)(v), (j)(3)(G)).

c. Post-Approval Requirements and Labeling Changes

Once FDA approves a drug, it can be sold only under the approved application's terms—including its labeling. Nonetheless, the statute imposes post-approval requirements on both branded and generic companies. Those obligations again differ for NDA and ANDA holders.

i. Branded Drugs

FDA commonly requires NDA holders to conduct follow-up clinical studies after they begin selling the product. 21 C.F.R. § 314.510; FDA, *Guidance for Industry: Postmarketing Studies and Clinical Trials—Implementation of Section 505(o) of the Federal Food, Drug, and Cosmetic Act*, at 2-3 & nn.3-4 (July 2009). In addition, NDA holders typically survey the worldwide scientific literature, and otherwise must review, investigate, analyze, and disclose to FDA any relevant information they discover (including information contained in the adverse reports they receive regarding any version of the product). 21 U.S.C. § 355(k); *see also* 21 C.F.R. § 314.80(b) ("Each applicant having an approved application under § 314.50 or, in the case of a 505(b)(2) application, an effective approved application [*i.e.*, an NDA approved under either 21 U.S.C. § 355(b)(1) or *id.* § 355(b)(2)], shall promptly

review all adverse drug experience information obtained or otherwise received ... from any source, foreign or domestic, including information derived from commercial marketing experience, post-marketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers."); *id.* §§ 314.80(c)-(k) (specific duties for NDA holders).

Due to those rigorous requirements, NDA holders acquire practically all relevant safety and efficacy data *before* the product's patent protection expires and the drug becomes eligible for generic competition.[6] Indeed, the post-approval review

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[6] Notably, patent expiration does not necessarily open the door to generic approvals. To help maintain incentives for branded companies to innovate and to provide a window during which NDA holders can thoroughly review postmarketing safety data before generics are approved, Hatch-Waxman bars the submission of an ANDA for several years after NDA approval. 21 U.S.C. § 355(j)(5)(F); *see also* Subcomm. Hearings, Pet. App. 118 (explaining that "[b]ecause the innovator manufacturer is familiar with the preapproval testing, it is in a good position to evaluate the adverse reactions," and arguing that "there should be a preeligibility period ... during which ANDA's would not be permitted" so that NDA holders can analyze post-approval data). Congress also recognized that FDA's review process often consumes years of the NDA holder's patent term. Hatch-Waxman therefore included patent-term extension provisions that effectively extend drug patents for the length of time during which an NDA was under review. 35 U.S.C. § 156; *see also Hoechst Aktiengesellschaft v. Quigg*, 917 F.2d 522 (Fed. Cir. 1990). As a result, it is not unusual for a branded drug to be on the market for more than a decade before generic versions are approved.

provisions ensure that almost all risks not discovered during the original clinical trials become known within a few years. Accordingly, FDA's regulations always have compelled NDA holders "to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association," 21 C.F.R. § 201.57, and brand companies often make such changes within a few years of approval. That was the case here—when the original Reglan® labeling was modified in 1985 to reflect information about tardive dyskinesia. *Infra* at 21-22.

The procedures for making these changes are set forth in 21 C.F.R. § 314.70, which includes both the Prior Approval Supplement ("PAS") and Changes Being Effected ("CBE") procedures. In addition, brand manufacturers occasionally send post-approval correspondence regarding their products to physicians and other healthcare professionals; these are typically referred to as "Dear Doctor letters."

(a) The PAS Procedure

The PAS procedure covers "major changes" to an approved application, and—as its name suggests—requires manufacturers to submit a supplemental application seeking FDA's "prior approval" before making significant changes to an approved product. *See* 21 C.F.R. § 314.70(b). Those changes include certain labeling modifications, but the PAS provision expressly "except[s]" labeling changes "described in paragraphs (c)(6)(iii), (d)(2)(ix), or (d)(2)(x)" of the regulation. *Id.* § 314.70(b)(2)(v)(A).

Because the cross-referenced paragraphs include changes to "add or strengthen a contraindication, warning, precaution, or adverse reaction," *id.*

§ 314.70(c)(6)(iii)(A), manufacturers may not use a PAS to propose new warnings. Instead, the procedure expressly is limited to labeling changes necessitated by post-approval modifications, such as those to "the qualitative or quantitative formulation of the drug product, including inactive ingredients," *id.* § 314.70(b)(2)(i), that were listed on the original labeling, *see id.* § 201.57(c)(12)(i)(c) (requiring product labels to disclose "qualitative and/or quantitative ingredient information").

(b) The CBE Procedure

Since 1965, FDA has permitted NDA holders to revise product labeling unilaterally to "add" or "strengthen" a "contraindication, warning, precaution, or adverse reaction" without prior approval through the CBE procedure. 21 C.F.R. § 314.70(c)(6)(iii). As this Court recently explained:

> Generally speaking, a manufacturer may only change a drug label after the FDA approves a supplemental application. There is, however, an FDA regulation that permits a manufacturer to make certain changes to its label before receiving the agency's approval. Among other things, this 'changes being effected' (CBE) regulation provides that if a manufacturer is changing a label to 'add or strengthen a contraindication, warning, precaution, or adverse reaction' or to 'add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product,' it may make the labeling change upon filing its supplemental application with the FDA; it need not wait for FDA approval.

Wyeth v. Levine, 129 S. Ct. 1187, 1196 (2009) (quoting 21 C.F.R. §§ 314.70(c)(6)(iii)(A), (C)).

Like PAS submissions, NDA holders must submit CBE supplements to FDA for ultimate approval, *see* 21 C.F.R. § 314.70(c)(7), and FDA may accept, modify, or reject CBE changes. *Id.*

(c) Dear Doctor Letters

A third way that branded manufacturers may disseminate information about their drugs—including updated warnings—is through direct correspondence to health care providers, commonly called Dear Doctor letters. *See* 21 C.F.R. § 200.5 (setting standards for such correspondence); Center for Drug Evaluation & Research, Manual of Policies & Procedures ["MAPP"] § 6020.10 (July 2, 2003) (establishing protocols for FDA review of such correspondence). Such letters are a regulated form of "labeling" under the statute, regulations, and caselaw. *See* 21 U.S.C. § 321(m) (labeling includes "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." 21 U.S.C. § 321(m); *see also Kordel v. United States*, 335 U.S. 345, 350 (1948) ("One article or thing is accompanied by another when it supplements or explains it.... No physical attachment one to the other is necessary."); 21 C.F.R. § 202.1(a)(l)(2). Accordingly, Dear Doctor letters are subject to the substantive standards that govern all labeling, including the law's misbranding provisions.

ii. Generic Drugs

In contrast to NDA holders, FDA may not require ANDA holders to conduct post-approval clinical

studies as a condition of approval. *See* 21 U.S.C. § 355(j)(2)(A) ("The Secretary may not require that an abbreviated application contain information in addition to that required by clauses (i) through (viii)."). Nor do FDA's regulations subject generic applicants to the same postmarketing surveillance, review, and data-collection obligations as NDA holders. Instead, ANDA holders are required only to forward to FDA the safety information they actually receive (including information regarding the adverse event reports they receive directly, and less detailed reports of other incidents they happen to hear about) and maintain adequate records. 21 C.F.R. § 314.98(a) (subjecting ANDA holders only to "the requirements of § 314.80 *regarding the reporting and recordkeeping of adverse drug experiences*," rather than the "review," "scientific literature," and "postmarketing studies" provisions of § 314.80) (emphasis added).

While ANDA holders may use the PAS and CBE processes to propose or effectuate certain labeling changes—most notably, *to conform* their product labeling to branded labeling that the NDA holder has changed—FDA always has made clear that generics may *not* use those mechanisms *to deviate* unilaterally from the branded warnings: "[T]he agency wishes to remind ANDA applicants that, as noted in paragraph 4 above, the labeling for an ANDA product must, with few exceptions, correspond to that for the reference listed drug." 57 Fed. Reg. at 17955, Pet. App. 105a (emphasis

added)[7]; *see also id.* at 17961 ("After ANDA approval, FDA tracks the labeling status of the pioneer drug product and, if necessary, notifies ANDA holders when and how they must revise their labeling."); Center for Drug Evaluation & Research ["CDER"], *Guidance for Industry: Changes to an Approved NDA or ANDA* ["*Changes Guidance*"] at 24 (Apr. 2004) ("All labeling changes for ANDA products must be consistent with section 505(j) of the Act.") (reproduced in Br. for the United States As *Amicus Curiae* at 2a, *PLIVA, Inc. v. Mensing* (Nos. 09-993, 09-1039)); CDER, *Guidance For Industry: Revising ANDA Labeling Following Revision of the RLD Labeling* ["*Revisions Guidance*"] at 5-6 (May 2000), Pet. App. 149-150a (explaining that "[t]he sponsor of an ANDA is ... responsible for ensuring that the labeling contained in its application is the same as the currently approved labeling of the [branded drug]," and instructing ANDA holders to "submit revised labeling" when "changes [are] needed because of approved changes to the [branded] labeling").

Consistent with this longstanding interpretation, FDA's regulations authorize FDA to revoke a prior approval if the ANDA product bears labeling that "is no longer consistent with that for the listed drug." 21 C.F.R. § 314.150(b)(10).

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[7] FDA's reference to "paragraph 4" incorporated the Agency's explicit rejection of a comment proposing "that FDA accept ANDA's with warnings or precautions in addition to those on the reference listed drug's label." *See* 57 Fed. Reg. at 17953, Pet. App. 103a-104a.

B. Facts and Proceedings

1. Metoclopramide

Metoclopramide is a dopaminergic blocking agent used principally for the short-term treatment of gastroesophageal reflux disease and diabetic gastroparesis. FDA first approved the drug on December 30, 1980, and the A.H. Robins Company began marketing it as Reglan®. In the few years immediately following FDA approval, post-marketing data revealed that long-term Reglan® use was associated with an involuntary movement disorder called tardive dyskinesia ("TD"). *See* GAO, *FDA Drug Review: Postapproval Risks 1976-85* ("GAO Review"), at 111 (April 1990).[8] In 1985, a new warning was added to the Reglan® labeling:

> Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with metoclopramide. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients are likely to develop the syndrome. Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase with the duration of treatment and the total cumulative dose.
>
> Less commonly, the syndrome can develop after relatively brief treatment periods at low

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[8] *Available at* http://archive.gao.gov/d24t8/141456.pdf.

> doses; in these cases, symptoms appear more likely to be reversible.
>
> There is no known treatment for established cases of tardive dyskinesia although the syndrome may remit, partially or completely, within several weeks-to-months after metoclopramide is withdrawn. Metoclopramide itself, however, may suppress (or partially suppress) the signs of tardive dyskinesia, thereby masking the underlying disease process. The effect of this symptomatic suppression upon the long term course of the syndrome is unknown. Therefore, the use of metoclopramide for the symptomatic control of tardive dyskinesia is not recommended.

PHYSICIAN'S DESK REFERENCE at 1660 (39th ed. 1985). The product's package insert also was revised to warn that "[t]herapy longer than 12 weeks has not been evaluated and cannot be recommended." *Id.*

In 2004, the metoclopramide labeling was revised again. Although the section on TD remained the same, the following sentence was added to the "Indications and Usage" section: "The use of Reglan® tablets is recommended for adults only. Therapy should not exceed 12 weeks in duration." Reglan® Label, Indications and Usage at 6, *at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/17854s047lbl.pdf (last visited January 23, 2011).[9]

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[9] As set forth in the companion brief filed by petitioners Actavis Inc. and Actavis Elizabeth LLC, further modifications

2. The Parties

Petitioners manufactured or distributed FDA-approved generic metoclopramide products. There is no dispute that the warnings on petitioners' products were at all relevant times the same as those on Reglan®—that is, that each petitioner's products bore the TD warnings set forth above, including the statements indicating that metoclopramide should not be taken for more than 12 weeks.

Respondent Gladys Mensing alleges that she ingested metoclopramide products manufactured by petitioners PLIVA, Inc., Teva Pharmaceuticals USA, Inc., UDL Laboratories, Inc., and Actavis Elizabeth LLC from March 2001 until March 2005 to treat diabetic gastroparesis. *Mensing* Amend. Compl. ¶¶ 27-36, JA180-81. She claims that she was diagnosed with TD in September 2005, and alleges that long-term metoclopramide use caused her injuries. *Id.* ¶ 37, JA181-82.

Respondent Julie Demahy alleges that she ingested metoclopramide products manufactured by petitioner Actavis Inc. from October 2002 to April 2007. *Demahy* Compl. ¶¶ 8-10, JA434-35. She claims that she was diagnosed with TD in October 2007, and likewise alleges that long-term metoclopramide use caused her injuries. *Id.* ¶ 13, JA435.

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were made to the product warnings regarding TD in 2009—well after the events giving rise to these cases.

3. The *Mensing* Litigation[10]

Mensing sued petitioners in the U.S. District Court for the District of Minnesota. Her complaint alleged that petitioners' metoclopramide warnings inadequately disclosed the risk of TD, and asserted that state-law obligated petitioners to provide different warnings in order to avoid liability. *Mensing* Amend. Compl. ¶¶ 110, 113-15, 117, 123-24, 127, 131, 133, 149, 178, 181 (JA198-204, 208, 214-15).

The district court granted petitioners' motion to dismiss these failure-to-warn claims on federal preemption grounds, ruling that "it would be impossible for [petitioners] to abide by both state and federal laws." *Mensing v. Wyeth, Inc.*, 562 F. Supp. 2d 1056, 1065 (D. Minn. 2008), JA383. The court first held that the CBE process does not allow generics to depart from the branded warnings, and that Mensing's claims thus posed a Hobson's choice: "[Petitioners] would be forced to choose between complying with the federal law while being exposed to state tort liability, or unilaterally adding a heightened warning to their labels at the risk of exposing themselves to federal liability." *Id.*

The district court likewise rejected Mensing's argument that petitioners could have proposed to change their warnings through the PAS process. JA384. As the district court explained, that argument impermissibly hinged on speculation,

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[10] Petitioners incorporate by reference the Actavis petitioners' recitation of the *Demahy* proceedings.

because FDA would have had to approve the warnings before they could have reached Mensing. JA383-84 ("The outcome of any such request to make a revision is uncertain and would require speculation as to what the FDA might have done.").

Finally, the court recognized that generic manufacturers may not send "Dear Doctor" letters that effectively alter product warnings. JA384. Requiring petitioners to do so would "directly conflict with the statutory scheme," *id.*, and any claim that petitioners should have asked FDA to send such a letter likewise would require impermissible "speculation over what the FDA might have done if [petitioners] had requested such a letter." JA385.

The Eighth Circuit reversed. It acknowledged that "generic labels must be substantively identical to the name brand label even after they enter the market." JA409. But it rejected petitioners' preemption defense, asserting that federal law at least would have allowed them to "*propose[]* a label change that the FDA could ... impose uniformly on all metoclopramide [products] if approved." JA410 (emphasis in original).

In the court's view, 21 C.F.R. § 201.57(e) compels each generic manufacturer to "take steps to warn its customers when it learns it may be marketing an unsafe drug," *id.*, and generic manufacturers can comply with that mandate through the PAS process. JA412. The court therefore deemed the CBE regulation "immaterial to the preemption analysis in light of this clear directive to generic manufacturers and the availability of the prior approval process." *Id.*

Despite conceding that the PAS procedure is subject to "exceptions including permissive use of the CBE process for warning enhancements," JA412-13 (citing 21 C.F.R. § 314.70(b)(2)(v)(A)), the court rejected petitioners' argument that those limitations precluded use of the PAS process to change product warnings. Instead, it argued, the PAS provision states that permissible "changes include, but are not limited to" the ones described in the rule, and thus does not actually "prevent generic manufacturers from proposing changes to a label's warning" through a PAS. JA412.

Finally, the court acknowledged that "Congress did not intend that generic manufacturers send out 'Dear Healthcare Provider' letters [unilaterally]" but nonetheless asserted that petitioners "could have suggested that the FDA send out a warning letter to health care professionals." JA413 & n.5. Because federal law thus did not "forbid [petitioners] from taking steps to warn their customers," the appellate court rejected their impossibility defense and declared:

> The generic defendants were not compelled to market metoclopramide. If they realized their label was insufficient but did not believe they could even propose a label change, they could have simply stopped selling the product. Instead, they are alleged to have placed a drug with inadequate labeling on the market and profited from its sales. If Mensing's injuries resulted from their failure to take steps to warn their customers sufficiently of the risks of taking their drugs, they may be held liable.

JA416.

SUMMARY OF ARGUMENT

The Hatch-Waxman Act expressly provides that the labeling on branded products and their generic equivalents—including any warnings—must be "the same." FDA's implementing regulations reiterate that command, and further make clear that it applies both before and after FDA first approves a generic product for sale. The Agency's duly promulgated, legally binding regulations are entitled to substantial deference, and any other approach to the statutory scheme would produce chaos: Potentially dozens of products that purport to have *the same* safety profile could bear *different* safety information, leaving physicians and patients with the false impression that generic drugs are not as safe as their branded equivalents (or each other). The Hatch-Waxman Act's sameness mandate thus preempts any state-law claim that petitioners' generic product warnings should have deviated from those on brand-name Reglan®; petitioners could not simultaneously comply with the federal requirement *to be the same* and a state-law duty *to deviate*.

The appellate courts nonetheless held that petitioners lawfully could have deviated from the Reglan® warnings by using the CBE or PAS processes, or by sending a Dear Doctor letter. Those holdings are erroneous.

Contrary to the Fifth Circuit's holding in *Demahy*, the CBE process does not allow generic manufacturers to depart from the branded product warnings. That process instead is available to generic companies so that they can quickly update their labeling *to match* any changes the brand manufacturer has implemented. *Demahy* thereby

turns the CBE provisions upside down, and in the process causes them to directly contradict the statutory and regulatory sameness requirements—in violation of the cardinal rule that laws "must be construed and applied so as to bring them into substantial harmony, not into square conflict." *Kotteakos v. United States*, 328 U.S. 750, 775 (1946). Federal law thus preempts any state-law claim that petitioners were obligated to deviate from the branded warnings by using the CBE process in ways FDA consistently has deemed to be prohibited.

Both appellate courts erred in holding that petitioners could have altered their products' warnings through the PAS process. That process does authorize manufacturers to request FDA's prior approval to make certain labeling changes. But it specifically "except[s]" the very kinds of changes respondents assert state law required—namely, changes to "add or strengthen a contraindication, warning, precaution, or adverse reaction." Because federal law thus bars petitioners from using the PAS process to propose such changes, state-law claims based on petitioners' failure to use that process are preempted.

The lower courts did, however, properly hold that federal law did not allow petitioners to send "Dear Doctor" letters that effectively would have altered the warnings for their generic products. It is well-settled that such correspondence is a regulated form of labeling, and Dear Doctor letters therefore must meet the same substantive requirements applicable to all other labeling—including the sameness standard for generic product warnings.

Nonetheless, the appellate courts erred in holding that federal law would not preempt state-law failure-to-warn claims that stem from petitioners' failure to "take steps" to modify their product warnings—whether by asking FDA to send a Dear Doctor letter, or otherwise "suggesting" that FDA modify the branded and generic product warnings. Such claims necessarily would require fact finders to speculate about what FDA would have done (and when it would have done so) if petitioners had made hypothetical "suggestions" to the Agency at a particular point in time. After all, causation is an essential element in any failure-to-warn claim—and failing to make "suggestions" to FDA could have caused respondents' injuries *only if* respondents can prove (among other things) that FDA would have exercised its exclusive authority to implement the suggested warnings in a timely fashion. This Court, however, long ago held that such speculative state-law claims impermissibly usurp the federal agency's authority. *Arkla*, 453 U.S. at 578-579.

Further, litigating the question of what FDA would have done in a hypothetical regulatory proceeding inevitably would undermine FDA's ongoing public-health mission by drawing its personnel into nationwide litigation—as the government has explained. *See, e.g., Warner-Lambert* Federal Br. at 7-8 ("[A] legal [claim] that turned on such speculation would inevitably lead parties to request burdensome and intrusive discovery from FDA concerning its approval of a drug, and thereby divert the agency from its core public health mission.").

And apart from these problems, such speculative claims would *by design* inundate FDA with a deluge of submissions—even though ANDA sponsors generally do not have the data needed to support such submissions, and even though FDA never has required such submissions. Yet *Buckman* held that plaintiffs may *not* pursue state-law causes of action predicated on claims that a regulated entity should have made submissions *to FDA*, because such claims would produce "a deluge of information that the Administration neither wants nor needs, resulting in additional burdens on the FDA's evaluation of an application. As a result, the comparatively speedy [abbreviated approval] process could encounter delays, which would, in turn, impede competition." *Buckman*, 531 U.S. at 351. That is precisely the case here.

At bottom, then, state-law "taking steps" claims would unleash precisely "the kind of direct impact on the United States, which preemption is designed to protect from undue incursion," *id.* at 351 n.6 (internal quotation omitted), and federal law therefore preempts "taking steps" claims as well.

ARGUMENT

I. FEDERAL LAW PREEMPTS STATE-LAW CLAIMS THAT PETITIONERS WERE OBLIGATED TO DEVIATE UNILATERALLY FROM THE BRANDED PRODUCT WARNINGS.

This case falls within the heartland of the Court's conflict-preemption jurisprudence. Respondents' state-law failure-to-warn claims allege that petitioners' metoclopramide warnings did not adequately disclose the risk of TD, and assert that

petitioners were obligated to alter those warnings—even though there is no dispute that petitioners' product warnings were at all times the same ones FDA approved for brand-name Reglan®.

Federal law, however, expressly prohibits generic companies (like petitioners) from unilaterally deviating from the branded product warnings—and thereby precluded petitioners from fulfilling any alleged state-law duty to deviate from the Reglan® warnings. Those explicit federal requirements necessarily trump the conflicting state law duties giving rise to respondents' failure-to-warn claims. *Hillsborough County, Fla. v. Automated Med. Labs., Inc.*, 471 U.S. 707, 713 (1985) ("[S]tate law is nullified to the extent that it actually conflicts with federal law."); *see also Geier v. American Honda Motor Co. Inc.*, 529 U.S. 861, 873 (2000) (state law preempted where it "penalizes what federal law requires"); *AT&T Co. v. Central Office Tel., Inc.*, 524 U.S. 214, 221-26 (1998) (state law preempted where it requires what federal law forbids); *Florida Lime & Avocado Growers, Inc. v. Paul*, 373 U.S. 132, 142-43 (1963) (state law preempted where "compliance with both federal and state regulations is a physical impossibility").

Respondents nonetheless have asserted that petitioners had three ways to change their warnings without violating federal law: (1) the CBE process; (2) the PAS process; and/or (3) sending "Dear Doctor" letters. Those arguments are wrong as a matter of law: None of those avenues would have allowed petitioners to change their product warnings, which under federal law must be "the same as" those on the branded product. Because respondents' claims seek

to punish petitioners for failing to do what federal law prohibited them from doing—and to hold them liable for having done what federal law required them to do—those claims are preempted.

A. Branded and Generic Product Warnings Must Be "The Same" At All Times.

The Hatch-Waxman Act expressly requires that each ANDA "show that the labeling proposed for the [generic] drug is *the same as* the labeling approved for the listed drug" with certain differences not relevant here. 21 U.S.C. § 355(j)(2)(A)(v) (emphasis added). Moreover, the statute expressly prohibits FDA from approving an ANDA if "the application is insufficient to show that the labeling proposed for the [generic] drug is *the same as* the labeling approved for the listed drug." *Id.* § 355(j)(4)(G) (emphasis added).

FDA has implemented those statutory provisions through formal notice-and-comment rulemaking. Like the statute, the Agency's duly-promulgated regulations require that generic "[l]abeling (including the container label, package insert, and, if applicable, Medication Guide) proposed for the drug product must be *the same as* the labeling approved for the [branded] drug." 21 C.F.R. § 314.94(a)(8)(iv) (emphasis added). They also make clear that FDA "will refuse to approve an abbreviated application [where it] is insufficient to show that the labeling proposed for the drug is *the same as* the labeling approved for the listed drug." *Id.* § 314.127(a)(7) (emphasis added).

Accordingly, there is no dispute that a generic product's warnings must be identical to its branded equivalent's warnings on the date FDA first approves

the generic drug. *Demahy*, JA535; *Mensing*, JA409. The lower courts nonetheless disagreed about whether the sameness requirement applies *after* the initial approval. While *Mensing* held that "generic labels must be substantively identical to the name-brand label *even after they enter the market*," JA409, *Demahy* asserted that "the statutory scheme is silent as to the manufacturer's obligations after the ANDA is granted" and claimed that FDA's regulations "do not address post-approval modifications at all." JA535. Indeed, *Demahy* declared, FDA's regulations "require only that a generic's label initially conform to the listed drug's." *Id.*

That is incorrect. *Demahy* based its assertions on the statutory and regulatory term "abbreviated application," which it construed to include only the document generic companies use to obtain an initial approval. JA534. But that interpretation directly conflicts with FDA's regulations. Indeed, in a regulation *Demahy* failed even to cite, FDA defined the term "abbreviated application" as "the application described under [21 C.F.R.] § 314.94, *including all amendments and supplements*." 21 C.F.R. § 314.3(b) (emphasis added). Accordingly, the sameness requirement applies throughout the life of the generic product. As FDA's regulations elsewhere make clear, ANDA holders must submit a "supplement" in order to alter a previously approved ANDA, *id.* § 314.97, and post-approval generic products thus equally are subject to the requirement

that their warnings be "the same as" the branded product's. *Id.* § 314.94(a)(8)(iv).[11]

Indeed, FDA's regulations provide for the revocation of a prior approval if the ANDA's "labeling ... is *no longer* consistent with that for the listed drug." *Id.* § 314.150(b)(10) (emphasis added; relied upon by *Mensing*, JA409). That provision obviously applies only *after* the initial FDA approval; there is no approval to revoke until one has been granted.

FDA's implementing regulations are entitled to substantial deference. Even if the Fifth Circuit were correct that the statute itself is "silent as to the manufacturer's obligations after the ANDA is granted," *Demahy*, JA534-35, Congress "left a gap for the agency to fill" by making "an express delegation of authority to the agency to elucidate a specific provision of the statute by regulation. Such legislative regulations are given controlling weight unless they are arbitrary, capricious, or manifestly contrary to the statute." *Chevron U.S.A., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 843-44

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[11] FDA consistently has explained that the regulations mean what they say. Indeed, when the Agency first proposed them, it *expressly rejected* comments proposing that the regulations be modified to allow generic product labeling "to deviate from the labeling for the reference listed drug to add contraindications, warnings, precautions, adverse reactions, and other safety-related information." *See* 57 Fed. Reg. at 17961, Pet. App. 108a-109a ("FDA disagrees with the comments. Except for labeling differences due to exclusivity or a patent and differences under section 505(j)(2)(v) of the act, the ANDA product's labeling must be the same as the listed drug product's labeling because the listed drug product is the basis for ANDA approval.") (citing 21 U.S.C. § 355(j)(2)(A)(v)).

(1984); *see also Auer v. Robbins*, 519 U.S. 452, 457-58 (1997).

The Agency's regulations do not come close to failing *Chevron*'s generous standard, and neither respondents nor the *Demahy* court even tried to argue that they do. There are good reasons for that. The statutory sameness requirements that apply to "abbreviated applications" form a comprehensive package that covers the chemical compound, its route of administration, its dosage form, its strength, its bioequivalence, and its labeling. 21 U.S.C. § 355(j)(2)(A). Construing the term "abbreviated application" so that those requirements apply *only before* initial ANDA approval effectively would allow ANDA holders to unilaterally alter *any* of these characteristics the day after FDA first grants approval—and thus to begin marketing products that FDA has never evaluated or approved despite the litany of sameness requirements that the statute and regulations apply to every "abbreviated application." *See id.*; 21 C.F.R. § 314.94.

At the same time, allowing generic manufacturers to unilaterally deviate from the branded product warnings after approval (not to mention imposing a state-law *duty* to do so) would produce a patchwork of distinct safety warnings for drugs that have the same safety profile. Two patients taking the same drug could receive different warnings if their respective physicians relied upon package inserts from different manufacturers. A single patient could receive different warnings if he or she switched physicians, or if a single physician relied upon a different company's package insert when renewing a prior prescription. Those results simply cannot be

squared with the basic premise underlying the statute: As FDA long ago recognized, only "[c]onsistent labeling will assure physicians, health professionals, and consumers that a generic drug is as safe and effective as its brand-name counterpart." 57 Fed. Reg. at 17961, Pet. App. 109a (citing 21 U.S.C. § 355(j)(2)(A)(v)).

At bottom, FDA's regulations sensibly reject the approach adopted by the *Demahy* court—which even *Mensing* recognized as having no basis in law or logic. JA409 ("[G]eneric labels must be substantively identical to the name-brand label even after they enter the market.").

B. Petitioners Could Not Have Used The CBE Process To Deviate From The Branded Product Warnings.

Demahy offered no rationale for its curious belief that generic companies are free to deviate from the brand-name product the day after FDA first approves an ANDA. Instead, it held that other FDA regulations somehow silently override the explicit sameness requirements set forth in both the statute and regulations. More specifically, *Demahy* asserted that *all* drug manufacturers are "subject to the requirement that their labeling 'be revised ... as soon as there is reasonable evidence of an association of a serious hazard with a drug,'" JA537 & n.57 (quoting 21 C.F.R. § 201.80(e) (alteration in original)), and then held that the CBE process is available for generic manufacturers to fulfill that alleged requirement. JA540-53. That analysis is flawed at both ends.

1. 21 C.F.R. § 201.80(e) Does Not Require ANDA Holders To Deviate From The Branded Product Warnings By Using The CBE Process.

At the threshold, § 201.80(e) demonstrably does *not* require ANDA holders to revise their warnings before the NDA holder modifies the branded product warnings. As *Wyeth* recognized, that regulation charges *the brand manufacturer* "both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market," by declaring that the brand manufacturer must "revise its label 'to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug.'" *Wyeth*, 129 S. Ct. at 1198 (quoting 21 C.F.R. § 201.80(e)).

There are good reasons for imposing those requirements on brand manufacturers. Branded companies conduct the original clinical studies, perform postmarketing studies, and are subject to extensive post-approval surveillance obligations. *Supra* at 14-16 & n.6. Those duties give the branded company access to virtually all clinical data on the product; all world literature regarding the product; and years (sometimes decades) of adverse event reports from all sources since the branded drug first was approved. Brand manufacturers thus are able to place the information they acquire in context, review and analyze its significance, and then craft a suitable labeling change based on "*sufficient evidence* that the standards [for such changes] are met." *Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical*

Devices—Final Rule, 73 Fed. Reg. 49603, 49605 (Aug. 22, 2008) (emphasis added).

By contrast—and by design—generic companies lack the NDA holder's comprehensive data, and thus cannot put the limited post-approval information they actually receive[12] in context: A single adverse event report generated years after approval hardly justifies wholesale labeling revisions absent a thorough understanding of the prior clinical data. *See, e.g.*, 73 Fed. Reg. at 49604 ("[T]he causal relationship between a product and an adverse effect is often difficult to establish and may require large trials, often specifically designed to assess the risk."); *see also Wyeth*, 129 S. Ct. at 1197 (noting that "risk information accumulates over time" and suggesting that "subsequent developments" might have meaning only in light of "'reports previously submitted to FDA'") (quoting 73 Fed. Reg. at 49607).

As a result, FDA has never interpreted § 201.80 (or its predecessor at § 201.57) as obligating generic manufacturers to deviate from the branded product warnings. To the contrary, the Agency has made clear that generic manufacturers comply with these regulatory provisions *by ensuring that their labeling is the same as the branded manufacturer's labeling at all times*. FDA promulgated § 201.80 in 2006, when

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[12] As FDA has observed, generic applicants rarely receive adverse reports since most are submitted to the brand manufacturer or FDA directly. *See* MAPP § 5240.8 (Nov. 1, 2005) (noting that "OGD [FDA's Office of Generic Drugs] receives few AERs [adverse event reports] or similar reports since the reports may not specify a generic manufacturer for the drug product").

it renumbered prior § 201.57 in the course of establishing distinct labeling requirements for drugs approved *before 2001*, *see* 21 C.F.R. § 201.56(b)(2) (pre-2001 drugs governed by the renumbered version of § 201.57 in new section § 201.80), and those approved *after 2001*, *see id.* § 201.56(b)(1) (post-2001 drugs governed by new § 201.57).[13] Among other things, the regulations for post-2001 drugs require labeling to include more than 30 categories or subcategories of information not specifically required of pre-2001 drugs. *Compare* 21 C.F.R. § 201.57 (new requirements) *with id.* § 201.80 (old requirements).

When FDA addressed these provisions in its 2000 rulemaking proposal, the Agency made clear that these provisions apply to brand manufacturers alone—and that they in no way supplant the specific sameness requirements that always have applied to generic drugs. In a section titled "Implementation of Proposed Content and Format Revisions to Products Approved or Submitted for Approval Under an ANDA," the Agency explained:

> Under [the statute and] the agency's regulations, the labeling of a drug product

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[13] *See also* Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products—Final Rule, 71 Fed. Reg. 3922, 3923 (Jan. 24, 2006) ("The agency proposed that older approved drug products would not be subject to these proposed changes. These older products would, instead, be subject to the labeling requirements at proposed § 201.80. The agency proposed to redesignate then-current § 201.57 as § 201.80 to describe labeling requirements for older drugs and add new § 201.57 to describe labeling requirements for new and recently approved drugs.").

> submitted for approval under an ANDA *must be the same as the labeling of the listed drug referenced in the ANDA*.... Thus, whether a [generic] drug product ... will be required to have labeling that complies with the final rule *will depend on the status of the labeling of the listed drug referenced in the ANDA*.

Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels—Proposed Rule, 65 Fed. Reg. 81082, 81098 (Dec. 22, 2000) (emphasis added; citing 21 U.S.C. § 355(j)(2); 21 C.F.R. §§ 314.94(a)(8), 314.127(a)(7)).

The 2006 Final Rule reiterated that explanation:

> As indicated in the proposed rule, the implementation plan for revised labeling for products approved or submitted for approval under an ANDA depends on the labeling of the listed drug referenced in the ANDA. In accordance with § 314.94(a)(8) (21 CFR 314.94(a)(8)), the labeling of a drug product submitted for approval under an ANDA must be *the same as* the labeling of the listed drug referenced in the ANDA.

71 Fed. Reg. at 3928 (emphasis added).

Suffice it to say, FDA's explicit statements that the branded requirements set forth in §§ 201.57 and 201.80 do not override the generic sameness requirements in §§ 314.94(a)(8)(iv) and 314.127(a)(7) fatally undermine *Demahy*'s conclusion that the former provisions somehow obligate ANDA holders to deviate from the branded warnings, whether through the CBE procedure or otherwise. *See, e.g.*,

Auer, 519 U.S. at 461 (citing *Robertson v. Methow Valley Citizens Council*, 490 U.S. 332, 359 (1989)); *see also Coeur Alaska, Inc. v. Southeast Alaska Conservation Council*, 129 S.Ct. 2458, 2474 (2009) (deferring to agency's effort to "harmonize [its] regulations" and make them "consistent with the regulatory scheme as a whole").

2. The CBE Process Does Not Otherwise Permit ANDA Holders To Deviate From The Branded Product Warnings.

Nor is there any basis for *Demahy*'s assertion that generic companies otherwise are permitted to use the CBE process to do what FDA's regulations elsewhere prohibit—that is, to deviate from the branded product's warnings. The Fifth Circuit seemed to think the CBE provision's language somehow supported that understanding:

> [T]he CBE regulation ... does not, on its face, distinguish between generic and name brand drug manufacturers; that is, it does not forbid a generic manufacturer from using the CBE process to unilaterally change a label. Located at 21 C.F.R. § 314.70, the regulation provides that "the holder of an approved application"—not just an approved new drug application—"may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change."

JA543 (quoting 21 C.F.R. § 314.70(c)(6)).

But that does not answer the question of *what kinds of changes* a generic manufacturer may make through the CBE regulation. Instead, FDA long ago made clear that generic manufacturers can only use

the CBE regulation to conform their warnings to updated branded warnings—as petitioners did when the Reglan® warnings were changed. *See Revisions Guidance*, Pet. App. 149a-50a, 151a ("The sponsor of an ANDA is ... responsible for ensuring that the labeling contained in its application is *the same as* the currently approved labeling of the RLD.... ANDA labeling changes needed because of approved changes to the labeling of the RLD may be submitted as a Special Supplement—Changes Being Effected.") (emphasis in original).

Any other interpretation would draw the CBE regulation into direct conflict with both the statute itself and 21 C.F.R. §§ 314.94(a)(8)(iv) and 314.127(a)(7), which all require generic product warnings to be "the same as" those on the branded equivalent. After all, CBE changes must be accompanied by a "supplement" detailing the changes imposed by the manufacturer. *See* 21 C.F.R. § 314.70(c)(6) ("[T]he holder of an approved application may commence distribution of the drug product involved *upon receipt by the agency of a supplement for the change*.") (emphasis added). And as explained earlier, the sameness requirements that apply to any "abbreviated application" by definition apply to any post-approval "supplement." *Id.* § 314.3(b) ("Abbreviated application means the application described under § 314.94, *including all amendments and supplements to the application*.") (emphasis added).

Demahy's interpretation of the CBE provision therefore violates the cardinal rule that laws "must be construed and applied so as to bring them into substantial harmony, not into square conflict."

Kotteakos, 328 U.S. at 775; *see also Pittsburgh & Lake Erie R. Co. v. Railway Labor Execs.' Ass'n*, 491 U.S. 490, 510 (1989) ("We should read federal [laws] 'to give effect to each if we can do so while preserving their sense and purpose.'") (quoting *Watt v. Alaska*, 451 U.S. 259, 267 (1981)); *cf. United Sav. Ass'n of Tex. v. Timbers of Inwood Forest Assocs., Ltd.*, 484 U.S. 365, 371 (1988) ("A provision that may seem ambiguous in isolation is often clarified by the remainder of the statutory scheme—because the same terminology is used elsewhere in a context that makes its meaning clear, *or because only one of the permissible meanings produces a substantive effect that is compatible with the rest of the law.*") (emphasis added).

That explains why FDA consistently has interpreted the CBE provision to *promote consistency* and *preclude deviations* between the branded and generic product labeling. *See, e.g.*, 57 Fed. Reg. at 17961; *Changes Guidance* at 2a ("All labeling changes for ANDA products must be consistent with section 505(j) of the Act."); *see also Revisions Guidance*, Pet. App. 149-151a. Again, FDA's settled interpretation of its own regulations is entitled to substantial deference—and neither respondents nor the *Demahy* court provided any basis for failing to accord the Agency's longstanding construction of its regulations the virtually conclusive deference to which it is due. *See, e.g., Coeur Alaska*, 129 S.Ct. at 2474; *Auer*, 519 U.S. at 461.

Because respondents' CBE-based state-law claims thus seek to punish petitioners for failing to do what federal law forbids, such claims are squarely preempted. *See Geier*, 529 U.S. at 881; *AT&T*, 524

U.S. at 221-26; *Hillsborough County*, 471 U.S. at 713; *Fla. Lime & Avocado Growers*, 373 U.S. at 142-43.

C. Petitioners Could Not Have Employed The PAS Process To Alter The Warnings On Their Product Labels.

Despite their apparent disagreement about the CBE procedure's availability, both appellate courts concluded that petitioners could have used the PAS process to propose different warnings. *Demahy*, JA551-52 ("Nor does anything ... explicitly forbid generic manufacturers from proposing a label change through the so-called prior approval process."); *Mensing*, JA412 ("[N]othing ... explicitly forbids [ANDA holders] from proposing a label change through the prior approval process.").

Both courts erred on this point. Though the PAS process does allow submissions seeking prior approval for certain labeling changes, *supra* at 17 (providing examples), it specifically excepts changes that otherwise would be covered by the CBE regulation. In particular, it authorizes proposed "[c]hanges in labeling, *except those described in paragraphs (c)(6)(iii), (d)(2)(ix), or (d)(2)(x) of this section*." *Id.* § 314.70(b)(2)(v)(A) (emphasis added). Because cross-referenced § 314.70(c)(6)(iii) includes the CBE provision covering changes "[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction," the PAS provision's "except" clause expressly precludes PAS submissions to request warning revisions like those respondents are seeking.

The appellate courts nonetheless deemed that interpretation of the PAS provision "too restrictive,"

Mensing, JA412, because the PAS provision "repeatedly uses the nonrestrictive phrase '[t]hese changes include, but are not limited to' in order to describe the changes manufacturers can propose." *Id.*; *see also Demahy*, JA552 ("[T]he regulations governing labeling changes repeatedly use the nonrestrictive phrase '[t]hese changes include, but are not limited to' in describing the changes manufacturers may propose"). Indeed, *Demahy* asserted, "there is no indication of an agency policy ... to prevent generic manufacturers from proposing *any and all labeling changes* ... through the prior approval process." JA552 (emphasis added).

That conclusion is demonstrably incorrect. The "except" clause in § 314.70(b)(2)(v) is the clearest possible indication that the PAS process cannot be used for certain labeling changes—namely, those "described in paragraphs (c)(6)(iii), (d)(2)(ix), or (d)(2)(x)." 21 C.F.R. § 314.70(b)(2)(v)(A). And construing the non-labeling-specific phrase "changes include, but are not limited to," *id.* § 314.70(b)(2), as overriding the labeling-specific "except" clause in § 314.70(b)(2)(v) otherwise violates two core canons of interpretation: that "the specific governs the general," *Long Island Care at Home, Ltd. v. Coke*, 551 U.S. 158, 170 (2007) (citing *Morales v. Trans World Airlines, Inc.*, 504 U.S. 374, 384-385 (1992); *Simpson v. United States*, 435 U.S. 6, 15 (1978)), and that laws "should be construed ... so that no part will be inoperative or superfluous, void or insignificant." *Corley v. United States*, 129 S.Ct. 1558, 1566 (2009) (quoting *Hibbs v. Winn*, 542 U.S. 88, 101 (2004) (itself quoting 2A N. Singer, STATUTES AND STATUTORY CONSTRUCTION § 46.06, pp. 181-186 (rev. 6th ed. 2000))).

Because the PAS process thus does not allow ANDA holders to seek different warnings, any state-law claim that petitioners were obligated to use that process is preempted. *See Geier*, 529 U.S. at 881; *AT&T*, 524 U.S. at 221-26; *Hillsborough County*, 471 U.S. at 713; *Fla. Lime & Avocado Growers*, 373 U.S. at 142-43.[14]

D. Petitioners Could Not Have Sent A "Dear Doctor" Letter That Effectively Would Have Altered Their Product Warnings.

The appellate courts properly concluded that generic manufacturers may not unilaterally send "Dear Doctor" letters that effectively alter their FDA-mandated product warnings. *Demahy*, JA553 ("[G]eneric manufacturers cannot send 'Dear Doctor' letters without prior FDA approval."); *Mensing*, JA413 n.5 ("Congress did not intend that generic manufacturers send out 'Dear Healthcare Provider' letters uncoordinated with other manufacturers of the drug.").

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[14] Even if the PAS process were available, there is another problem with that argument. As discussed in greater detail below (*infra* § II.A), merely submitting a PAS would not itself fulfill the alleged state-law duty to provide an adequate warning, because FDA would have had to approve the proposed warning before it could have been delivered to respondents. 21 C.F.R. § 314.70(b)(3) ("The applicant must obtain approval of a supplement from FDA prior to distribution of a drug product made using a change under paragraph (b) of this section."). Accordingly, such state-law failure-to-warn claims would necessarily—and impermissibly—depend on speculation about how FDA would have exercised its exclusive authority. *See infra* § II.

That is so, as both courts recognized, because Dear Doctor letters are a form of product labeling, 21 C.F.R. § 202.1, and must conform to the substantive standards for labeling detailed earlier. *See Mensing*, JA413 n.5 ("The letters are considered regulated labeling.") (citing 21 C.F.R. § 202.1); *Demahy*, JA552 ("These letters—addressed to medical professionals and intended to explain the risks associated with prolonged use of metoclopramide—would also be subject to FDA regulation because they fall within the agency's broad definition of 'labeling.'") (quoting 21 C.F.R. §§ 202.1; citing 21 C.F.R. § 200.4).

Accordingly, any state-law claim that petitioners were obligated to send Dear Doctor letters of the sort envisioned here likewise are preempted. *Geier*, 529 U.S. at 881; *AT&T*, 524 U.S. at 221-26; *Hillsborough County*, 471 U.S. at 713; *Fla. Lime & Avocado Growers*, 373 U.S. at 142-43.

II. FEDERAL LAW PREEMPTS STATE-LAW CLAIMS THAT PETITIONERS WERE OBLIGATED TO "SUGGEST" THAT FDA ALTER THE PRODUCT WARNINGS.

Perhaps recognizing the flaws in respondents' CBE, PAS, and Dear Doctor theories, the lower courts went further—holding that petitioners at least could have "*tak[en] steps* to warn their customers" without violating federal law, and that failure-to-warn claims stemming from petitioners' alleged failure to do so would not be conflict-preempted. *See, e.g.*, *Mensing*, JA414 (emphasis added). The courts identified two such pathways:

(1) that petitioners "*could have suggested*" that FDA send Dear Doctor letters, even if petitioners could not have sent such

letters on their own, *id.* (emphasis added); *Demahy*, JA553; and

(2) that petitioners *could have asked* FDA to change the labeling for both the branded and generic drugs, even if petitioners could not have effectuated such changes on their own, *Mensing*, JA410-11; *Demahy*, JA537-38.[15]

Petitioners freely concede that neither the Hatch-Waxman Act nor FDA's regulations prohibit them from "suggesting" that FDA consider sending Dear Doctor letters or that the Agency otherwise reconsider the warnings for both branded and generic products. Indeed, the First Amendment would render any such restriction unenforceable. *See, e.g., First Nat'l Bank of Boston v. Bellotti*, 435 U.S. 765, 791 n.31 (1978). But *state-law* claims that effectively seek to hold generic manufacturers liable for failing to make such "suggestions" *to a federal agency* are no less preempted than the claims addressed earlier.

This Court long ago held that federal law preempts state-law claims that depend on speculation about how a federal agency would have

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[15] While both courts identified steps that federal law would have allowed petitioners to take, neither court cited authority for the proposition that state law embraces failure-to-warn claims that necessarily depend on a third party's action (here, FDA) in order to fulfill the duty to provide adequate warnings. Instead, the courts appear to have assumed that such contingent claims are viable. *Mensing*, JA414; *Demahy*, JA557-58.

exercised its powers in hypothetical regulatory proceedings, because such claims necessarily usurp the agency's authority. *See Arkla*, 453 U.S. at 578-579; *see also Nantahala Power & Light Co. v. Thornburg*, 476 U.S. 953, 963-964 (1986); *Chicago & N.W. Transp. Co. v. Kalo Brick & Tile Co.*, 450 U.S. 311, 324-27 (1981). Actually trying such claims would impose significant burdens on both FDA and its decision-making personnel. And this Court likewise has held that state-law claims are preempted where their enforcement would directly interfere with a federal regulatory regime or where they necessarily derive from federal regulatory requirements. *Buckman*, 531 U.S. at 351-53; *Geier*, 529 U.S. at 873; *Gade v. National Solid Wastes Mgmt. Ass'n*, 505 U.S. 88, 108 (1992); *Felder v. Casey*, 487 U.S. 131, 138 (1988). Those authorities are controlling here.

A. State-Law "Taking Steps" Claims Usurp FDA's Authority Because They Depend On Speculation About How FDA Would Have Exercised Its Exclusive Powers.

In direct contrast to the traditional failure-to-warn claims at issue in *Wyeth*, the "taking steps" claims hypothesized by the appellate courts here necessarily depend on speculation about how FDA would have responded to a hypothetical submission seeking warning changes for all metoclopramide products. This Court, however, long ago made clear that "the Supremacy Clause will not permit" state-law claims that are "necessarily supported by an assumption" that a federal agency "would have approved [a request]," because such claims "usurp[] a

function that Congress has assigned to a federal regulatory body." *Arkla*, 453 U.S. 480-82.

That problem arises in this context, because there is a critical gap in any failure-to-warn claim alleging that petitioners should have "taken steps" to alter their product warnings: Merely "suggesting" that FDA *consider* making a warning change that it *might* apply to both branded and generic products would not itself fulfill the state-law duty to provide an adequate warning, because the suggestion alone cannot ensure that the requested warnings would have reached respondents before they were prescribed and took metoclopramide. Instead, the Agency would have had to analyze, evaluate, and act favorably on the "suggestions" before petitioners could have delivered the new warnings.

As the lower courts expressly conceded, FDA's independent action is therefore an essential element in the causal chain necessary to prevail on a hypothetical "taking steps" claim. *Mensing*, JA410 ("[T]he generic defendants could have at least proposed a label change that the FDA *could* receive and impose uniformly on all metoclopramide manufacturers *if approved*.") (emphasis added); *see also Bruzer v. Danek Med., Inc.*, No. Civ. 3-95-971/RHKJMM, 1999 WL 613329, at *8 n.10 (D. Minn. Mar. 8, 1999) (holding that plaintiffs bear the "burden of showing that the Defendants' negligence proximately caused their injuries"); *Schafer v. JLC Food Sys., Inc.*, 695 N.W.2d 570, 574 (Minn. 2005) (plaintiffs bear the burden of proving causation in negligence cases); *Bilotta v. Kelley Co.*, 346 N.W.2d 616, 623 n.3 (Minn. 1984) (same for strict-liability cases); *cf. Buckman*, 531 U.S. at 353 (Stevens, J.,

concurring) ("As the Court points out, an essential link in the chain of causation that respondent must prove in order to prevail is that, but for petitioner's fraud, the allegedly defective orthopedic bone screws would not have reached the market.").

That problem does not arise in a typical failure-to-warn case, where the defendant could have changed its product warnings unilaterally. In such cases, the plaintiff need not prove that a third party—here, FDA—would have approved the warnings. Therefore, the plaintiff in such cases ordinarily needs to show only that (a) the drug is responsible for his or her injuries and (b) the existing warning's alleged inadequacy proximately caused the drug use that precipitated those injuries. That essentially is what *Wyeth* recognized when it held that the brand manufacturer could have fulfilled its alleged state-law duties by using the CBE process to send new warnings. 129 S. Ct. at 1199 ("Wyeth has failed to demonstrate that it was impossible for it to comply with both federal and state requirements. The CBE regulation permitted Wyeth to unilaterally strengthen its warning.").

Here, by contrast, petitioners could *not* have changed their warnings unilaterally through the CBE procedure, *supra* § I.A, or by sending a Dear Doctor letter. *Supra* § I.C. The PAS procedure is not available to propose new warnings, but in any case runs through FDA. *Supra* § I.B. And assuming *arguendo* that petitioners otherwise could have "suggested" that FDA take action, respondents can prove that petitioners' failure to do so caused their injuries *only* by showing that FDA would have approved a *hypothetical* request for a *hypothetical*

change on a *hypothetical* record after *hypothetical* consultations with affected parties at a *hypothetical* point in time. JA383-84 ("The outcome of any such request to make a revision is uncertain and would require speculation as to what the FDA might have done."); *cf. Whitmore v. Arkansas*, 495 US 149, 159-60 (1990) ("It is just not possible for a litigant to prove in advance that the judicial system will lead to any particular result in his case.").

The appellate courts sought to deflect those concerns by invoking *Wyeth* for the proposition "that uncertainty about the FDA's response to such measures makes federal preemption less likely. '[A]bsent clear evidence that the FDA would not have approved a change to [the drug's] label, we will not conclude that it was impossible for [the manufacturer] to comply with both federal and state requirements.'" *Mensing*, JA414 (quoting *Wyeth*, 129 S.Ct. at 1198; alterations in original); *Demahy*, JA555-56 ("What the FDA might have done once Actavis suggested these changes is immaterial to the imposition of liability; *Levine* makes plain that uncertainty about the FDA's response makes federal preemption less likely."). The appellate courts thus held that "[t]o support preemption the generic defendants must show the likelihood of FDA *in*action." *Mensing*, JA414-15 (emphasis original); *Demahy*, JA556.

There are two problems with that assertion. First, *Wyeth* compels the opposite result here. In that case, the Court's CBE holding meant that the brand manufacturer unilaterally could have altered its product warnings in the first instance. 129 S. Ct. at 1198 ("[T]he CBE regulation permitted [Wyeth] to

provide such a warning before receiving the FDA's approval"). That effectively obviated the causation question embedded in these cases, because it meant the brand manufacturer's new warnings could have reached consumers without FDA action and thus that the manufacturer could comply simultaneously with both its state and federal duties. While the brand manufacturer in *Wyeth* nonetheless speculated that FDA might have rescinded a CBE change, it was perfectly natural for this Court to place the burden of proof on the party advancing speculative claims about a change in the status quo—there, the brand manufacturer. *Id.* at 1198-99.

In these cases, however, petitioners could *not* have delivered new warnings to consumers without FDA action. Thus, consistent with *Wyeth*'s allocation of burdens, respondents properly bear the burden of proving a speculative claim about FDA's potential reaction to a hypothetical labeling-change request. Indeed, given that causation is an essential element of the plaintiff's case-in-chief, it would make no sense to place the burden of disproving this critical element on the defendant.

Perhaps more important, the appellate courts focused on the wrong question. Allocating the burden of proof for showing preemption at the pretrial phase does not fix the causation problem in this context, because the eventual trial of a "taking steps" claim *necessarily* depends on speculation about what a federal agency would have done in hypothetical proceedings. But as *Arkla* recognized, the trial of such state-law claims unavoidably usurps the federal agency's exclusive authority. *See, e.g.*, *Arkla*, 453 U.S. at 578-82.

That well-settled principle controls here, and *Arkla* is directly on point. In *Arkla*, plaintiff Hall contracted to sell natural gas to Arkla at a specified rate, but the parties' contract also included a "most favored nation" clause: If Arkla purchased gas from another entity at a higher price, Hall also would receive the higher price. *Id.* at 573. The Federal Power Commission ("FPC") signed off on the rate specified in the parties' contract, *id.* at 574, and Arkla later paid a higher rate to a third party. Arkla did not, however, increase its payments to Hall, who responded by filing a traditional state-law breach-of-contract action. The Louisiana Supreme Court ultimately awarded Hall damages equal to the difference between the rate specified in his Arkla contract and the price Arkla paid the third party. *Id.* at 574.

This Court reversed, holding that Hall's breach-of-contract claims were preempted. *Id.* at 578-579. As the Court explained, federal law prohibited parties from charging gas rates that were not pre-approved by FPC, so the plaintiff's claim and the state court's verdict *necessarily* presumed that FPC would have approved the rates effectively awarded to Hall as damages. *Id.* at 580-581. Yet "the Commission alone is empowered to make that judgment, and until it has done so, no rate other than the one on file may be charged." *Id.* at 581. By thus awarding Hall damages based on speculation about how FPC might have exercised its authority in hypothetical proceedings, the court had "usurped a function that Congress has assigned to a federal regulatory body." *Id.* at 582; *see also Nantahala*, 476 U.S. at 963-964; *Kalo Brick*, 450 U.S. at 324-27.

That is precisely the case here. Because federal law explicitly prohibits ANDA holders from modifying their warnings without FDA pre-approval (whether through the PAS procedure or otherwise), a state-law verdict predicated on a "taking steps" theory necessarily would presume FDA's approval of the proposed new warning. Yet as set forth above, it is FDA's prerogative—and FDA's prerogative alone—to make that decision.

B. Litigating Such Claims Would Draw FDA Into Nationwide Litigation And Thereby Undermine Its Public-Health Mission.

Moreover, actually litigating the question of how FDA might have responded to a hypothetical request would impose extraordinary burdens on the Agency, to the detriment of its public-health mission—burdens that simply were not implicated in *Wyeth* given the Court's holding that brand manufacturers may use the CBE procedure to augment their warnings unilaterally. *See Wyeth*, 129 S. Ct. at 1199. As the government previously explained to this Court, litigating how FDA would have responded to a hypothetical request necessarily requires access to the record before the Agency at the time the request allegedly should have been made. *See, e.g.*, Transcript of Record at 25, *Warner-Lambert* (No. 06-1498), 2008 WL 495030 [the "*Warner-Lambert* Tr."] ("[I]f you were going to seriously litigate the question, you would have to know—in order to put this in context, to determine things like withholding and materiality—you'd have to know everything that FDA had before it, what FDA thought was required as part of that process."). But neither personal-

injury plaintiffs nor generic defendants have access to that record. Only FDA has that information.

Accordingly, the parties in hypothetical "taking steps" cases would have to subpoena FDA's records, ensnarling Agency officials with discovery in hundreds—perhaps thousands—of cases around the country. It is hard to overstate the burden that would impose on FDA or its interference with the Agency's public-health mission. *See, e.g., Warner-Lambert* Federal Br. at 22-23 ("In one recent products liability class action, *Walson v. Merck & Co.*, No. 3:04-cv-00027-GPM-DGW (S.D. Ill.), FDA devoted approximately 1,300 employee hours to producing approximately 40,000 pages of documents in response to a third-party subpoena. Private litigation such as this would divert FDA's resources and create a substantial potential for distorting its mission."); *see also* Br. for the United States As *Amicus Curiae* in Support of Petitioner at 10-11, *Buckman* (No. 98-1768), 2000 WL 1364441 [the "*Buckman* Federal Br."] (noting that such claims "invite highly intrusive discovery" and "therefore pose a real danger of diverting FDA's resources from the important health mission that Congress has assigned to it and of distorting FDA's internal decision-making process"). Not surprisingly, FDA has contested such discovery in the past, though with mixed results. *See, e.g., Warner-Lambert* Federal Br. at 22-23.

Moreover, the record alone—assuming it could be pried from FDA's hands, and notwithstanding the confidentiality concerns the NDA holder might raise—cannot itself prove how FDA would have responded to a hypothetical submission at a

hypothetical point in time. Only FDA's personnel can speak to that question. So as the government again has explained to this Court, litigants will subpoena FDA officials to testify, diverting them from their federal responsibilities in order to bombard them with hypothetical questions. *Id.* at 21-22 ("Parties would likely seek ... discovery concerning the agency's internal deliberations, including agency officials' states of mind and the courses of action they might have taken under various hypothetical scenarios."); *Warner-Lambert* Tr. at 25 ("You would then have to, I suppose, depose FDA witnesses as to what ... decisions they might have made in hypothetical circumstances.").

Needless to say, the government has strongly resisted demands that public-health officials testify in private litigation. *See, e.g.*, Mot. to Quash Deposition Subpoenas at 11, *In re Viropharma, Inc. Sec. Litig.*, No. 202CV01627 (E.D. Pa. Mar. 9, 2004), 2004 WL 5618403 ("With a limited staff and budget, FDA could not continue to fulfill its mandate, per 21 U.S.C. § 393(b), to regulate the nation's supply of food, drugs, and medical devices while providing experts and witnesses for the myriad of private lawsuits involving one or more FDA-regulated products. Simply put, if private litigants could freely compel the attendance and testimony of FDA employees in litigation, FDA's mission of protecting the public from unsafe and ineffective products would inevitably be compromised by the diversion of its employees from their official duties."); Br. for the United States as *Amicus Curiae*, *Strong v. American Cyanamid Co.*, No. SC 88890 (Mo. Feb. 5, 2008), at 26 ("FDA officials are not at a private litigant's beck and call to testify."); *see also Moore v. Armour*

Pharm. Co., 927 F.3d 1194, 1197-98 (11th Cir. 1991) (affirming order quashing subpoena and explaining that "plaintiffs' interest in getting the deposition of Dr. Evatt simply cannot compare to the government's interest in maximizing the use of its limited resources in dealing with a national health crisis. Each day that Dr. Evatt and other doctors employed by the CDC spend giving deposition testimony is a day they are kept from doing research that might save numerous lives.").

That of course explains why the government consistently has opposed allowing plaintiffs to pursue these kinds of claims in past cases. *Warner-Lambert* Federal Br. at 7-8 ("Speculation by fact-finders about what FDA would have done in hypothetical circumstances invades the province of the agency. Moreover, a legal standard that turned on such speculation would inevitably lead parties to request burdensome and intrusive discovery from FDA concerning its approval of a drug, and thereby divert the agency from its core public health mission."); *Buckman* Federal Br. at 29 ("The prospect of such intrusive inquiries and attendant litigation would pose a significant potential for diverting FDA's resources from the important health mission that Congress has assigned to it and for distorting FDA's internal decisionmaking processes."). And it well illustrates why such claims should not be allowed to proceed here.

C. The Prospect Of "Taking Steps" Liability Would Undermine FDA's Ability To Administer The Regulatory Scheme By Causing ANDA Holders To Flood The Agency With Submissions.

Separate and apart from the distracting litigation burden these claims would impose on FDA, such claims would undermine FDA's ability to administer the regulatory scheme in other respects. As set forth above, FDA's regulations establish fundamentally distinct postmarketing requirements for brand manufacturers and generic manufacturers based on the recognition that generic manufacturers *by design* lack the information necessary to craft post-approval warning revisions. *See supra* 18-19. The prospect of break-the-bank tort litigation predicated on a "taking steps" theory, however, inevitably would disrupt this careful balance and undermine FDA's administration of the regulatory regime. After all, the possibility of state liability for failing to exceed the federal requirements would "cause applicants to fear that their disclosures to the FDA, although deemed appropriate by the Administration, will later be judged insufficient in state court. Applicants would then have an incentive to submit a deluge of information that the Administration neither wants nor needs, resulting in additional burdens on the FDA." *Buckman*, 531 U.S. at 351.[16]

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[16] Furthermore, claims based on allegations that ANDA holders failed to make required regulatory submissions would run directly counter to the Act's express prohibition against private rights of action grounded on such alleged violations. *See* 21 U.S.C. § 337(a).

Indeed, the submissions contemplated here would be both less useful and more burdensome than the ones *Buckman* feared. Even though generic companies do not acquire the data necessary to frame and substantiate a labeling change request, the threat of potential liability will create powerful incentives for generic companies to submit something—*anything*—to FDA after receiving even a single adverse event report, simply so that they can tout that submission as a defense in possible state tort litigation.

Such thinly supported submissions—potentially from dozens of companies, rather than from a single NDA holder with access to the universe of relevant data—would inundate FDA. As the government's CVSG brief made clear, FDA cannot ignore those submissions. Instead, the Agency's informal (and, until now, rarely invoked) procedures for handling such submissions would require FDA to initiate a high-priority and resource-taxing consultation process. CVSG Br. at 16 ("[I]ntra-agency consultations regarding ANDAs with possible serious safety concerns are assigned the highest priority.") (quotation omitted).

And while FDA is bogged down processing an unprecedented deluge of likely meritless labeling-change requests from companies seeking to deflect state-law liability, "the comparatively speedy [ANDA] process could encounter delays, which would, in turn, impede competition among predicate [drugs] and delay health care professionals' ability to prescribe [these products]." *Buckman*, 531 U.S. at 351; *see also Kobar v. Novartis Corp.*, 378 F. Supp. 2d 1166, 1173-74 (D. Ariz. 2005) (analogizing the

§ 510(k) process in *Buckman* to the drug-approval process, and explaining that *Buckman*'s concern with "the dilatory effect of encouraging manufacturers to submit a 'deluge' of information to the FDA, appl[ies] with equal, if not greater force, to the context of the drug approval process. As with medical devices, the public suffers when the FDA approval process is unnecessarily prolonged. As with medical devices, the public is adversely impacted when manufacturers are discouraged from seeking FDA approval of products out of fear of the inherent difficulty of complying with the 50 States' tort regimes. As with medical devices, when the costs of development and FDA approval increase, so does the ultimate price of the product.") (quotation omitted).

Given that the whole point of the Hatch-Waxman Act was to expedite generic approvals and reduce pharmaceutical costs, *Andrx*, 256 F.3d at 809; *Barr Labs.*, 930 F.2d at 76; *Glaxo*, 110 F.3d at 1568, such "taking steps" claims would—like the claims in *Buckman*—"exert an extraneous pull on the scheme established by Congress, and [are] therefore pre-empted by that scheme." *Id.* at 353.

CONCLUSION

The judgments should be reversed.

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RESPONDENT'S BRIEF

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IN THE

Supreme Court of the United States

PLIVA, INC., ET AL., *Petitioners*,

v.

GLADYS MENSING, *Respondent*.

ACTAVIS ELIZABETH LLC, *Petitioner*,

v.

GLADYS MENSING, *Respondent*.

ACTAVIS, INC., *Petitioner*,

v.

JULIE DEMAHY, *Respondent*.

On Writs of Certiorari to the United States Courts of Appeals for the Eighth Circuit and for the Fifth Circuit

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BRIEF FOR RESPONDENTS

In *Wyeth v. Levine*, --- U.S. ----, 129 S. Ct. 1187 (2009), this Court held that federal law does not preempt a state failure-to-warn claim brought against a prescription-drug manufacturer. These consolidated cases will resolve whether state failure-to-warn claims may be brought against the manufacturers of generic drugs. As every court to consider this issue since *Levine* has concluded, the answer is yes.[1]

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[1] *See Mensing v. Wyeth*, J.A. 400; *Demahy v. Actavis, Inc.*, J.A. 520; *Gaeta v. Perrigo Pharm. Co.*, No. 09-15001, 2011 WL 198420 (9th Cir. Jan. 24, 2011); *Vitatoe v. Mylan Pharm., Inc.*, No. 1:08cv85, 2010 WL 1008788 (N.D. W. Va. Mar. 5, 2010); *Weilbrenner v. Teva Pharm. USA, Inc.*, No. 7:08-CV-23, 2010 WL 924915 (M.D. Ga. Mar. 10, 2010); *Swicegood v. Pliva, Inc.*, No. 1:07-cv-1671, 2010 WL 1138455 (N.D. Ga. Mar. 22, 2010); *Dorsett v. Sandoz, Inc.*, No. CV06-7821, 2010 WL 1174204 (C.D. Cal. Mar. 26, 2010); *Finnicum v. Wyeth, Inc.*, No. 1:09-CV-785 (E.D. Tex. May 25, 2010); *Fulgenzi v. Wyeth, Inc.*, No. 5:09CV1767, 2010 WL 649349 (N.D. Ohio Feb. 19, 2010); *Munroe v. Barr Labs.*, 670 F. Supp. 2d 1299 (N.D. Fla. 2009); *Bartlett v. Mutual Pharm. Co.*, 659 F. Supp. 2d 279 (D.N.H. 2009); *Stacel v. Teva Pharm. USA*, 620 F. Supp. 2d 899 (N.D. Ill. 2009); *Schrock v. Wyeth*, 601 F. Supp. 2d 1262 (W.D. Okla. 2009); *Couick v. Wyeth, Inc.*, No. 3:09-CV-210-RJC-DSC, 2009 WL 4644394 (W.D.N.C. Dec. 7, 2009); *Pustejovsky v. Wyeth*, No. 4:07-CV-103-Y, 2009 WL 3336032 (N.D. Tex. Sept. 4, 2009); *see also In re Budeprion XL Marketing & Sales Litig.*, No. 09-md-2107, 2010 WL 2135625 (E.D. Pa. May 26, 2010) (rejecting preemption defense in consumer fraud class action against generic drug companies); *Kellogg v. Wyeth*, 612 F. Supp. 2d 437 (D. Vt. 2009) (post-*Levine* ruling denying certification for interlocutory appeal of pre-*Levine* ruling denying preemption). Long before *Levine*, the Fourth Circuit reached the same conclusion in *Foster v. American Home Prods. Corp.*, 29 F.3d 165, 170 (4th Cir. 1994).

Levine held that the manufacturer, not the Food and Drug Administration (FDA), bears primary responsibility for ensuring that labeling for its drug adequately warns of the product's risks. This conclusion applies equally to the manufacturers of generic drugs. Under the federal regulatory scheme, the manufacturer of a generic drug shares responsibility with the manufacturer of its brand-name counterpart to ensure that the labeling for both products adequately warns prescribers and protects consumers.

Defendants seek a special immunity from state tort liability for generic drug companies, an immunity that would create an arbitrary and irrational distinction between classes of patients based on the vagaries of pharmacy practice: those whose prescriptions were filled with brand-name products would retain their right to sue, while those whose pharmacies substituted generic drugs would lose that right. Not only would such a regime make no sense, but it would also create a disincentive for consumers to take generic drugs, which is precisely the opposite of what Congress intended when it passed the Hatch-Waxman Amendments to the Food, Drug, and Cosmetic Act (FDCA) in 1984. Try as they might, Defendants cannot muster any evidence that Congress ever intended such a bizarre result.

Today, seventy percent of prescriptions in this country are filled with generic drugs. And, contrary to Defendants' claims, the fact that a drug has "gone generic" does not mean that it is safe. In reality, as the facts of this case demonstrate, drug risks frequently do not become clear until years after a drug has been on the market. The drug that injured Gladys Mensing and Julie Demahy, for example, had

been available as a generic for more than fifteen years at the time it was first prescribed to them, and it was just two years ago that FDA finally mandated a "black box" warning of the risks of long-term use. If generic drug companies are granted immunity for failing to warn of known risks of their drugs, they will have very little incentive to strengthen their warning labels as new risks emerge, even though federal law mandates that they do so. The inevitable result will be more deaths and injuries that could easily have been prevented—a result that Congress did not intend and this Court should not countenance.

Defendants' main defense cannot withstand even the mildest scrutiny. They argue that it would have been "impossible" for them to warn consumers of their drug's risks without running afoul of federal regulations. Yet the United States itself has disavowed this theory Moreover, Defendants themselves concede that they could have told FDA about the mounting evidence that long-term use of their drug causes catastrophic injuries and asked the agency to approve a stronger warning. Ignoring this mounting evidence, Defendants chose to sit back and do nothing. They should not be rewarded with an immunity that would strip consumers of any means of seeking redress for their injuries.

PERTINENT STATUTORY AND REGULATORY PROVISIONS

Pertinent statutory and regulatory provisions are set forth in an Appendix to this brief.[2]

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[2] A number of regulations relevant to this case have been revised or redesignated over the past decade. This brief

STATEMENT OF FACTS

In March 2001, Gladys Mensing's doctor prescribed Reglan to treat her diabetic gastroparesis. J.A. 402. The active ingredient in Reglan is metoclopramide, which is available in both branded and generic forms. *Id.* Pursuant to Minnesota's drug substitution law, Minn. Stat. § 151.21, Ms. Mensing's pharmacist filled her prescriptions with generic metoclopramide. *Id.* The generic metoclopramide was manufactured by, *inter alia*, Defendants Pliva, Inc. (Pliva), Teva Pharmaceuticals USA, Inc. (Teva), UDL Laboratories (UDL), and Actavis Elizabeth LLC (Actavis). *Id.* at 391. Ms. Mensing took metoclopramide, as prescribed, for four years. *Id.* at 402.

Ms. Mensing's long-term use of metoclopramide caused her to develop tardive dyskinesia. *Id.* Tardive dyskinesia is a severe and irreversible neurological disorder, characterized by "grotesque involuntary movements of the mouth, tongue, lips, and extremities, involuntary chewing movements, and a general sense of agitation." *McNeil v. Wyeth*, 462 F.3d 364, 366 (5th Cir. 2006).

In 2002, Julie Demahy's doctor prescribed Reglan to treat her gastroesophageal reflux disorder (reflux). J.A. 434, 521. Ms. Demahy's pharmacist filled her prescriptions with generic metoclopramide

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follows the practice of *amicus curiae* United States in citing to the regulations in effect in 2001, the earliest year in which either of the Plaintiffs ingested the Defendants' products, noting subsequent changes where relevant. U.S. Amicus Br. 4 n.2. By contrast, Defendants' briefs cite to a number of revised versions of these same regulations that post-date the events here at issue.

in accordance with Louisiana's substitution statute, La. Admin. Code, Title 46, Part LIII, Chapter 25, § 2511. *Id.* The generic metoclopramide Ms. Demahy ingested was manufactured by Defendant Actavis, Inc. (Actavis). *Id.* Like Ms. Mensing, Ms. Demahy took metoclopramide, as prescribed, for approximately four years. *Id.* As a result of her use of metoclopramide she too developed tardive dyskinesia. *Id.*

Both Plaintiffs sued the manufacturers of the metoclopramide they had ingested. They asserted traditional state-law products liability claims for failure to warn. They alleged that the defendants had provided inadequate warnings regarding the risk of tardive dyskinesia from long-term metoclopramide use and that the absence of adequate warnings of that risk caused their injuries. J.A. 26, 439.[3]

In both cases, the generic drug company defendants moved to dismiss based on federal preemption. J.A. 402, 522.[4] On appeal from the district court rulings,[5] both the Fifth Circuit and the

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[3] Both plaintiffs also sued the manufacturers of brand-name Reglan for misrepresention. Those claims were abandoned or dismissed under state law because the Plaintiffs had never taken Reglan. J.A. 418-21, 478.

[4] To be precise, following the district court's grant of motions to dismiss by Pliva and Actavis in the *Mensing* case, the other generic defendants asserted preemption through motions for summary judgment, but on purely legal, not factual, grounds. J.A. 402-03. Actavis also filed a motion to dismiss in *Demahy*. J.A. 522.

[5] The appeal in *Demahy* was interlocutory, from a ruling denying the motion to dismiss. J.A. 518.

Eighth Circuit rejected the preemption defense, guided by this Court's *Levine* decision. J.A. 415-18, 562-63.

Regulatory History of Metoclopramide

Metoclopramide is a prokinetic gastrointestinal drug that enhances contractions of the esophagus, stomach, and intestines. It acts by blocking the body's dopamine receptors, thereby impeding the transfer of signals between nerves. As a "dopamine antagonist," metoclopramide can adversely affect the body's extrapyramidal system which controls fine motor skills. Tardive dyskinesia is a particularly severe form of such extrapyramidal symptoms (EPS). *See McNeil*, 462 F.3d at 366.

Reglan was first approved by FDA in 1980 as treatment "for two to eight weeks . . . for the relief of symptoms associated with acute and recurrent diabetic gastric stress." *See Physician's Desk Reference*, at 1566 (36th ed. 1982). In 1984 an indication for "short-term (4 to 12 weeks) therapy" for reflux was added. *Physician's Desk Reference*, at 1660 (39th ed. 1985); *see also Physician's Desk Reference*, at 1635 (41st ed. 1987). The following year, generic drug manufacturers, including the Defendants, began to obtain approval for generic versions of metoclopramide.[6]

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[6] Reglan was approved pursuant to a "New Drug Application" (NDA) under 1962 Food, Drug and Cosmetics Act § 505(b), 21 U.S.C. § 355(b) (FDCA), while the Defendants' metoclopramide products were approved through an "Abbreviated NDA" (ANDA) under 1984 FDCA § 505(j), 21 U.S.C. § 355(j), enacted as part of the Drug Price Competition & Patent Term Restoration Act, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (Hatch Waxman Amendments).

Although Reglan/metoclopramide was approved only for short-term use, many doctors prescribed the drug for longer periods because reflux and gastroparesis are chronic conditions. *See McNeil*, 462 F.3d at 369 (Wyeth's own data showed that 84 percent of patients were using Reglan long-term; 32 percent of patients in one study had been taking metoclopramide for more than one year); *see also* Reglan Label, *Warnings* at 5 (2010) (20 percent of patients using metoclopramide do so for more than 12 weeks).[7] Both Plaintiffs allege that manufacturers of generic metoclopramide were aware of this widespread long-term use but took no steps to discourage the practice.[8]

During all times relevant to these cases, the labels for Reglan and generic metoclopramide repeatedly asserted that the risk of EPS, including tardive dyskinesia, was quite low. The "Clinical Pharmacology" section of the label stated: "Like the phenothiazines and related drugs, which are also dopamine antagonists, metoclopramide produces sedation and may produce extrapyramidal symptoms, although these are comparatively rare (See WARNINGS)." Mensing 8th Cir. Opening Br. App. 260a. The "Warnings" section of the label elaborated:

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[7] *Available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/017854s055lbl.pdf (last visited Feb. 17, 2011).

[8] A drug is misbranded if its label "fails to reveal" material facts "with respect to consequences which may result from . . . customary or usual . . . use" of the drug, which includes common "off-label" uses. 21 U.S.C. §§ 321(n) and 352(a).

> Extrapyramidal symptoms, manifested primarily as acute dystonic reactions, occur in approximately 1 in 500 patients treated with the usual adult dosages of 30 to 40 mg'/day of metoclopramide. These usually are seen during the first 24 to 48 hours of treatment with metoclopramide, occur more frequently in pediatric patients and adult patients less than 30 years of age and are even more frequent at higher dosages.

Id. at 261a.[9]

The "Adverse Reactions" section of the label reiterated this characterization:

> **Extrapyramidal Reactions (EPS)**
>
> Acute dystonic reactions, the most common type of EPS associated with metoclopramide, occur in approximately 0.2% of patients (1 in 500) treated with 30 to 40 mg of metoclopramide per day.

Id.[10]

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[9] The "Warnings" section identified tardive dyskinesia, as one of the EPS that may develop in patients treated with metoclopramide, but implied that tardive dyskinesia will occur far less frequently than the far more readily treatable acute dystonic reactions, which the label identified as the "primar[y]" "manifest[ation]" of EPS. *Id.*

[10] Again, tardive dyskinesia was identified as a possible adverse reaction, but one that will occur in far fewer patients than the 1 in 500 who will experience acute dystonic reactions. *Id.*

This information about the risks of tardive dyskinesia and other EPS was first added to the Reglan/metoclopramide label in 1985. *Physician's Desk Reference*, at 1660 (39th ed. 1985); *Physician's Desk Reference*, at 1635 (41st ed. 1987). The labeling bore the same language regarding these risks until 2009.[11]

In the years between FDA approval of generic metoclopramide and Plaintiffs' use of the product, a number of studies in the medical literature concluded that the risk of tardive dyskinesia and other EPS associated with metoclopramide use was likely far greater than the 0.2 percent risk reflected on the label. *See McNeil*, 462 F.3d at 370 n.5 (citing studies from 1989, 1993, and 1994). Moreover, prior to mid-2003, at least 87 cases of metoclopramide-associated tardive dyskinesia had been reported to FDA's Adverse Event Reporting System (AERS), most involving long-term use of the product. Douglas Shaffer, *et al.*, *Tardive Dyskinesia Risks and Metoclopramide Use Before and After U.S. Market Withdrawal of Cisapride*, 44 J. Am. Pharm. Ass'n 661, 663 (2004).[12] Adverse event reports submitted to the AERS are publicly available and could have been

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[11] In 2004, FDA did approve the addition of a sentence to the "Indications and Usage" section of the label: "Therapy should not exceed 12 weeks in duration." Reglan Label, *Indications and Usage*, at 6 (2004), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/17854s047lbl.pdf.

[12] The authors note that only a small percentage of adverse drug events are spontaneously reported, *id.* at 664 (reporting rates between 1 and 13 percent), so the actual number of cases of metoclopramide-associated tardive dyskinesia would have been far higher.

obtained by the Defendants. 21 C.F.R. § 314.430(e)(4).

Despite the mounting evidence that the risk of tardive dyskinesia was far greater than reflected on the label, no manufacturer ever proposed to FDA that the warnings on the Reglan and generic metoclopramide labels be revised to reflect that greater risk. Nor did any manufacturer of metoclopramide alert health care professionals or patients that metoclopramide's labeling did not adequately convey the risk of tardive dyskinesia associated with long-term use. J.A. 406.

Finally, in 2009, FDA, acting on its own initiative pursuant to the Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (FDAAA), ordered manufacturers of Reglan and generic metoclopramide to add a "Boxed Warning" to their labels about the increased risk of tardive dyskinesia from long-term metoclopramide use. A Boxed Warning is the strongest warning prescribed by the federal regulations, short of contraindicating the use altogether. 21 C.F.R. § 201.57(e).

The Boxed Warning stated, *inter alia*, "Chronic treatment with metoclopramide can cause tardive dyskinesia, a serious movement disorder that is often irreversible . . . . Prolonged treatment (greater than 12 weeks) with metoclopramide should be avoided in all but rare cases where therapeutic benefit is thought to outweigh the risks to the patient of developing tardive dyskinesia." *See* Letter from Joyce Korvick, Deputy Dir. for Safety, Div. of Gastroenterology Products, Center for Drug Evaluation and Research (CDER), FDA, to NDA

holders for Reglan, 2 (Feb. 26, 2009) (hereinafter "Korvick letter");[13] *see also* Letter from Gary Buehler, CDER, FDA, to ANDA holders for Reglan, 2 (Feb. 26, 2009) (hereinafter "Buehler letter").[14] The FDA also ordered the manufacturers to add information in the warning section of the label that a published study had found tardive dyskinesia occurring in 20 percent of the patients treated for at least three months, *id.*, a hundred times greater than the 0.2 percent risk previously identified on the label.

At the same time it ordered these changes, FDA issued a MedWatch Safety Alert to health care professionals and a news release regarding the risk of tardive dyskinesia associated with long-term metoclopramide use. *See* FDA, *Metoclopramide-Containing Drugs* (Feb. 26, 2009).[15] The FDA took these steps because it "want[ed] patients and health care professionals to know about this risk so they can make informed decisions about treatment." FDA, *News Release* (Feb. 26, 2009).[16]

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[13] *Available at* http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM111376.pdf.

[14] *Available at* http://www.fda.gov/ downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM111378.pdf.

[15] *Available at* http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm106942.htm.

[16] *Available at* http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm149533.htm.

Federal Regulation of Drug Safety

The Drug Approval Process

All prescription drugs sold in this country require FDA approval before they may be marketed. The core objective of FDA approval process is to ensure that drugs are both safe and effective. *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 142 (2000). Manufacturers of new drugs must submit an NDA that demonstrates such safety and effectiveness through the results of clinical trials. 21 U.S.C. §§ 355(b), (d). NDA applicants must also propose labeling for the drug, which must identify, *inter alia*, appropriate use of the product, contraindications, warnings, precautions, and adverse reactions. 21 C.F.R. § 201.56. In particular, the drug's label must bear "such adequate warnings against use . . . where its use may be dangerous . . . as are necessary for the protection of users." 21 U.S.C. § 352(f)(2) (App. 1a).

Under the Hatch-Waxman Amendments, once a brand-name drug loses patent protection, another company may seek approval for a generic version of that drug through a process known as an abbreviated NDA or ANDA. 21 U.S.C. § 355(j). Because ANDA approval is based on the brand-name or "reference listed" drug (RLD), the proposed labeling for the generic drug must generally be the same as that for the RLD. 21 C.F.R. § 314.94(a)(8)(iv) (App. 15a). However, the proposed ANDA labeling is also subject to the statutory requirement that it bear "adequate warnings." 21 U.S.C. § 352(f)(2). In order to resolve any tension between these two requirements, FDA has instructed drug companies applying for an ANDA that, "if an ANDA applicant

believes new safety information should be added to a product's labeling, it should contact FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised." 57 Fed. Reg. 17950, 17961, cmt. 40 (Apr. 28, 1992).

Manufacturers' Post-Approval Obligations

Because pre-marketing clinical trials of branded drugs are typically quite small, involving only carefully selected patients taking the drug for limited periods of time, many serious risks associated with a drug are not discovered until a larger and more diverse population has been exposed to the drug and the drug has been on the market for a number of years. Karen E. Lasser, *et al.*, *Timing of New Black Box Warnings and Withdrawals for Prescription Medicines*, 287 JAMA 2215 (May 1, 2002) (finding that half of all black box warnings on drugs introduced after 1975 were added after the drug had been on the market for seven or more years). Often, as in this case, risks do not fully emerge until long after generic drugs have entered the market and captured a large percentage of sales. For this reason, FDA imposes numerous post-approval obligations on manufacturers of both brand-name and generic drugs to ensure products remain safe and effective as labeled. 21 U.S.C. § 355(k).

All drug manufacturers must conduct regular pharmacovigilance to stay current on information regarding their products and ensure that their products remain safe and effective as labeled. *See* 21 U.S.C. § 355(k). They must "promptly review all adverse drug experience information obtained . . . from any source, . . . including reports in the scientific literature" and submit adverse event

reports to FDA. 21 C.F.R. §§ 314.80 (App. 11a) (NDA holders) and 314.98(a) (App. 18a) (ANDA holders). Each year, they must report to FDA a "summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product" and they must describe to FDA "the actions the applicant has taken or intends to take as a result of this new information." 21 C.F.R. §§ 314.81(b)(2)(i) (App. 13a) (NDA holders) and 314.98(c) (ANDA holders).

Most importantly, both the RLD holder and generic drug manufacturers are subject to the requirement that their approved "labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved." 21 C.F.R. § 201.57(e).[17]

A drug company does not need to conduct extensive clinical research to support a new warning; "reasonable evidence of an association of a serious hazard with a drug" can come from adverse event reports or from studies in the medical literature, such as the published studies and adverse event reports discussed above, *supra*, p. 9, which had linked long-term metoclopramide use with tardive dyskinesia. *Levine*, 129 S. Ct. at 1197; J.A. 558-60. The FDA itself relied on published studies when it

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[17] In 2006, FDA issued amended labeling regulations for prescription drugs. 71 Fed. Reg. 3922 (Jan. 24, 2006). That rulemaking redesignated § 201.57(e) as 21 C.F.R. § 201.80(e) and it remains the regulatory standard for drugs labeled under the old rules, such as metoclopramide. 71 Fed. Reg. at 3988, 3996. A virtually identical requirement applies to drugs labeled under the new regulation. 21 C.F.R. § 201.57(c)(6). 71 Fed. Reg. at 3,990.

mandated the black-box warning for metoclopramide in 2009. *See* Korvick letter at 1-2; Buehler letter at 1-2.

Procedures for Updating Warnings of Drug Risks

A number of procedures are available to generic-drug manufacturers to update the warnings on drug labels to account for new evidence of a serious hazard associated with a drug and to notify health care professionals of these risks.

First, a generic drug manufacturer may fulfill its obligations under § 201.57(e) by contacting FDA's Office of Generic Drugs (OGD) to express its concern about the need for stronger warnings on both the brand-name and generic products. Brief of the United States as Amicus Curiae 15-17. After adopting its final rule implementing the Hatch-Waxman Amendments, FDA advised ANDA holders: "After approval of an ANDA, if an ANDA holder believes that new safety information should be added, it should provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised." 57 Fed. Reg. at 17961 cmt. 40. Such a communication from a generic drug company to the OGD triggers a "substantive evaluation" of the need for additional warnings under FDA operating procedures. U.S. Amicus Br. 15-17 (citing Center for Drug Evaluation & Research, *Manual of Policies & Procedures* 5200.6 (May 9, 2001) (MAPP)).

Alternatively, any drug manufacturer can seek a labeling change by filing a "supplemental application" to its NDA or ANDA in accordance with

21 C.F.R. § 314.70 (App. 8a); *see also* 21 C.F.R. § 314.97 (App. 17a) (making § 314.70 applicable to ANDA holders). There are two kinds of supplemental applications under § 314.70: 1) a prior approval supplement (PAS) which requires FDA approval before proposed changes can be implemented, 21 C.F.R. § 314.70(b); and 2) a "Changes Being Effected" supplement (CBE), under which a manufacturer may implement the proposed change at the same time as the supplement application is submitted to FDA, 21 C.F.R. § 314.70(c).[18]

A drug manufacturer may use either supplement process to obtain FDA approval for a new warning. In general, drug manufacturers use the PAS process, and obtain prior agency approval, for changes to a drug's approved labeling. 21 C.F.R. §§ 314.70(b) and (b)(3). However, FDA regulations expressly permit a change in the approved labeling "[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction" to be made through a CBE supplement. 21 C.F.R. §§ 314.70(c) and (c)(2)(i).

The CBE process developed out of the PAS process in 1965 so certain kinds of labeling changes are "placed into effect at the earliest possible time." The FDA will "take no action against a drug or applicant solely because" it had added a new

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[18] Every time a drug manufacturer, brand-name or generic, submits a supplement application, it must certify to FDA that it will "update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling." FDA, Form 356h (Oct. 2005), *available at* http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM082348.pdf.

warning to its approved labeling "prior to his receipt of a written notice of approval of the supplemental new-drug application." 30 Fed. Reg. 993-94 (Jan. 30, 1965). The agency adopted this policy of non-enforcement, which eventually became CBE, "in the interest of drug safety." *Id.* The FDA retains authority to reject labeling changes made through the CBE process. *Levine*, 129 S. Ct. at 1198.

A drug manufacturer can also request a labeling change through a Citizen Petition. 21 C.F.R. § 10.30 (App. 2a). The Citizen Petition process authorizes any person to request that FDA take formal agency action, including actions related to the safety of a prescription drug.[19] The Citizen Petition initiates an agency review of the proposed action. Both brand-name and generic drug companies frequently utilize the Citizen's Petition process.[20]

Besides changing approved labeling, drug manufacturers can ensure warning information is

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[19] *See, e.g.*, Letter from Janet Woodcock, M.D., Director, CDER, FDA, to James P. Reichmann (Feb. 17, 2011) (granting requested change in labeling for terbutaline regarding pregnancy risk), *available at* http://www.fda.gov/downloads/Drugs/DrugSafety/UCM243797.pdf; Letter from Steven K. Galson, M.D., M.P.H., Acting Director, CDER, FDA, to Sidney M. Wolfe, M.D., *et al.* (Aug. 9, 2005) (granting request to remove Meridia (sibutramine) from market due to safety risks), *available at* http://www.fda.gov/ohrms/dockets/dockets/02p0120/02p-0120-pdn0001-vol1.pdf.

[20] *See* FDA, Chronological Lists of Petitions and Advisory Opinions 2006-2008 (listing numerous petitions filed by drug companies), *available at* http://www.fda.gov/RegulatoryInformation/Dockets/UCM090522.htm, /UCM090519.htm, and /UCM090358.htm (last visited Feb. 22, 2011).

communicated directly to health care providers through "Dear Health Care Professional" (DHCP) letters. 21 C.F.R. § 200.5 (App. 5a). A drug manufacturer can request that FDA send out a DHCP letter[21] or it can issue one itself. Drug companies typically consult with FDA before sending their own DHCP letter, although the FDCA and FDA regulations do not prohibit drug companies from sending such correspondence unilaterally. U.S. Amicus Br. 17; *see also* 44 Fed. Reg. 37434, 37447 cmt. 63 (Jun. 26, 1979) ("the issuance of letters . . . warning health care professionals [about] possibly harmful adverse effects associated with the use of the drug . . . is not prohibited by these regulations"). DHCP letters are considered labeling under the Act, 21 U.S.C. § 321(m); nevertheless, because FDA classifies such letters as "promotional labeling," they are not subject to the "sameness" requirement applicable to "approved labeling." 21 C.F.R. § 201.100(d)(1).[22]

Thus, a number of procedures are available to generic drug companies to meet their obligations under 21 C.F.R. § 201.57(e) (App. 6a) to update their drugs' labeling with new warnings and to provide doctors with adequate warning regarding emerging risks of their drugs. As the Fifth Circuit emphasized, each of these procedures

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[21] *See, e.g.*, 21 U.S.C. § 355-1(i)(2) (establishing this process as a part of a risk evaluation and mitigation strategy under FDA Amendments Act of 2007).

[22] DHCP letters must contain a "true statement" about product risks, 21 C.F.R. § 201.100(d)(1), and must not be otherwise false or misleading. 21 U.S.C. § 352(a).

> shares the same fundamental attributes: the manufacturer bears primary responsibility for maintaining its label consistent with safe and effective use of its product; when reports indicate that a label requires revision, the manufacturer must alert the FDA and provide supporting scientific data; and the FDA then makes the decision whether such a labeling change is supported by science. . . . The federal interest is in maintaining safe and effective labeling that is consistent across name brand and generic bioequivalent versions of the same drug. *Who* prompts the FDA to consider necessary changes to that shared label is immaterial.

J.A. 554 (emphasis in original).

The Critical Role of Generic Drug Manufacturers in Ensuring Drug Safety

The generic drug industry has thrived under the regulatory regime established by Congress in the Hatch-Waxman Amendments. Today, over seventy percent of prescriptions are filled with generic drugs. Susan Okie, *Multinational Medicines—Ensuring Drug Quality in an Era of Global Manufacturing*, 361 New Eng. J. Med. 737, 738 (2009). Every state has enacted a drug substitution law that permits or requires pharmacies to fill a prescription written for a brand-name drug with its generic equivalent, absent a specific physician's instruction or consumer objection. Thomas P. Christensen, *et al.*, *Drug*

Product Selection: Legal Issues, 41 J. Am. Pharm. Ass'n 868, 869 (2001).

Because of their lower cost, generic drugs quickly capture the vast majority of sales of that product. Congressional Budget Office, *Effects of Using Generic Drugs on Medicare's Prescription Drug Spending*, at 7 (2010) (Over 90 percent of prescriptions for "multiple-source" drugs [available in branded and generic forms] are filled by generics.).[23] Unable to compete on price, RLD holders often actually or effectively abandon the market. GPhA, *Savings Achieved Through the Use of Generic Pharmaceuticals 2000-2009*, at 7 (2010) (32 percent of unique drug molecules with active sales are sold only as generics).[24] Wyeth, the manufacturer of Reglan, sold its NDA rights to a smaller company, Schwarz Pharma, Inc., Decl. of Jeff Siefert in Supp. of Schwarz Pharma Mot. for Summ. J. at 2, *Mensing v. Wyeth, Inc.*, 562 07-CV-3919 (D. Minn. 2008), ECF No. 99, and that company decided not to pay to continue publishing the Reglan label in the *Physician's Desk Reference*, presumably on account of declining sales. *See Physician's Desk Reference* (57th ed. 2003). If generic drug manufacturers did not share in responsibility for ensuring the adequacy of drug warnings, there would often be no one left "minding the store."

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[23] *Available at* http://www.cbo.gov/ftpdocs/118xx/doc11838/09-15-PrescriptionDrugs.pdf.

[24] *Available at* http://www.gphaonline.org/sites/default/files/GPhA%20Savings%20Study%20Book%20Updated%20Web%20FINAL%20Jul23%2010_0.pdf.

SUMMARY OF ARGUMENT

In *Wyeth v. Levine*, --- U.S. ----, 129 S. Ct. 1187 (2009), this Court held that federal law does not preempt state inadequate warning claims brought against prescription-drug manufacturers, "absent clear evidence that the FDA would not have approved" a stronger warning for a drug. *Id.* at 1198. At the core of the ruling was the Court's conclusion that

> it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. It is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market.

Id. at 1197-98.

These consolidated cases, before this Court on appeals from rulings on motions to dismiss for failure to state a claim, raise the issue whether federal law preempts the same state inadequate warning claims brought against manufacturers of generic drugs as a matter of law. Both the Fifth and the Eighth Circuit Courts of Appeals, guided by this Court's decision in *Levine*, ruled that it did not.

Congress did not intend to preempt state-law tort claims against generic drug companies. Congress's decision not to include an express preemption provision in the Hatch-Waxman Amendments, coupled with the absence of any federal remedy for persons injured by inadequately labeled drugs, demonstrates that Congress intended

to preserve state tort remedies as a complementary form of consumer protection.

Defendants' bid for conflict preemption on impossibility grounds is belied by the governing regulatory framework and by their own concessions. For defendants to prevail on this defense at this early procedural stage (*i.e.*, on motions to dismiss), they would have to demonstrate that it was impossible for them to have provided adequate warnings for their drug. But federal law, like state law, requires drug companies to provide adequate warnings about the dangers posed by their products and FDA regulations include a variety of procedural mechanisms through which Defendants could have sought FDA approval for stronger warnings. Defendants now concede that they could have asked FDA to approve stronger warnings for both Reglan and generic metoclopramide or to issue a DHCP letter about the risks associated with long-term use, but they chose not to do so.

Having made this concession, Defendants can only establish their impossibility preemption defense through "clear evidence that the FDA would not have approved a change" in warnings. *Levine*, at 1198. Defendants have not even attempted to make this showing and all evidence is to the contrary: when, in 2009, FDA learned on its own of the true risks associated with Reglan and metoclopramide, the agency ordered a new "Boxed Warning" for the drug. Equally as important, whether FDA would have denied approval for a stronger warning if Defendants had requested one is an issue of fact, inappropriate for resolution on a motion to dismiss.

Based on the disputed assumption that any warning change would have required prior agency approval, Defendants argue that it is Plaintiffs' burden to prove that FDA would have approved a warning change. But this argument mischaracterizes state law: to establish their claims for inadequate warning, Plaintiffs need only establish that Defendants sold metoclopramide with inadequate warnings regarding its risks, and that the absence of such adequate warnings caused their injuries. The burden of proving that FDA would have prohibited a stronger warning remains on Defendants as a necessary element of their impossibility preemption defense.

Defendants' argument for switching the burden of proof rests on a "fundamental misunderstanding" of *Levine*. Defendants contend that *Levine* turned on manufacturers' ability to warn "unilaterally" by virtue of the CBE process, and they argue that if their ability to warn is subject to prior FDA approval, then the Plaintiffs' claims are impliedly preempted. But *Levine* rested on the drug manufacturer's responsibility under federal law to maintain adequate warnings regarding its product's risks, not on the availability of one particular procedure for updating those warnings, the CBE process, which was not disputed. As this Court recognized, regardless of the process a manufacturer employs, FDA always retains the authority to approve or reject a labeling change. A preemptive conflict between state and federal law will only arise where a defendant can prove that FDA would have rejected a labeling change that state law requires.

Nor are the Plaintiffs' claims preempted on the ground that they obstruct statutory or regulatory

purposes. State tort remedies for inadequate warnings complement the federal regulatory scheme for generic drugs by helping to ensure that generic drugs remain safe as well as inexpensive. Drug risks often do not emerge until years after generic drugs have entered the market and captured the vast majority of sales and FDA lacks the resources to monitor the safety of all available drugs on its own. By providing incentives for generic drug manufacturers to pay attention to publicly available adverse event reports and scientific literature regarding the products they sell, and to go to FDA when such information reveals the need for additional warnings, state tort law plays a critical role in ensuring drug safety. By contrast, a ruling in favor of preemption would eliminate these incentives, increase health care costs, and undermine confidence in the safety and therapeutic equivalence of generic drugs. It would also leave Plaintiffs without remedy for their injuries.

Finally, Plaintiffs' claims are not preempted under the reasoning of either *Arkansas Louisiana Gas Co. v. Hall*, 453 U.S. 571 (1981), or *Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341 (2001). Pliva's argument that they are is again based on the false premise that Plaintiffs' claims are something other than traditional black-letter inadequate warning claims under state law. Moreover, neither case stands for the sweeping proposition for which Pliva cites it. *Ar La Gas* was a narrow holding about the exclusive authority of the Federal Power Commission to approve prices for natural gas under the "filed rate doctrine," while *Buckman* involved an unusual state law claim premised on fraud on FDA that this Court has been careful to distinguish from

traditional state tort law claims such as Plaintiffs assert here.

ARGUMENT

I. CONGRESS DID NOT INTEND TO PREEMPT STATE-LAW TORT CLAIMS AGAINST GENERIC DRUG COMPANIES.

"'[T]he purpose of Congress is the ultimate touchstone in every pre-emption case.'" *Levine*, 129 S. Ct. at 1194 (quoting *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996)). Congress made clear its intent about failure-to-warn claims when it decided not to include an express preemption provision in either the FDCA or the Hatch-Waxman Amendments. As this Court said in *Levine*: "If Congress thought state law suits posed an obstacle to its objectives, it surely would have enacted an express preemption provision at some point during the FDCA's 70-year history. . . . Its silence on the issue, coupled with its certain awareness of the prevalence of state tort litigation, is powerful evidence that Congress did not intend FDA oversight to be the exclusive means of ensuring drug safety and effectiveness." *Id.* at 1200.

The same conclusion applies to Defendants' preemption arguments here. As the Eighth Circuit observed:

> The Hatch-Waxman Amendments are part of this 70 year history and they do not explicitly preempt suits against generic manufacturers. Congress could have crafted a preemption provision for generic drugs in its 1984 amendments, having done so for medical devices less

> than 10 years earlier. It chose not to do that.

J.A. 407.

The *Levine* decision also makes clear that any consideration of congressional intent is subject to a strong presumption against preemption. 129 S. Ct. at 1194-95 & n.3. The States have long regulated public health and safety through their tort systems. When Congress legislates "in a field which the States have traditionally occupied, . . . we start with the assumption that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress." *Id.* at 1194-95 (quoting *Lohr*, 518 U.S. at 585, and *Rice v. Sante Fe Elevator Corp.*, 331 U.S. 218, 230 (1947) (internal quotations omitted)).

The bar to a finding that Congress intended to take away Plaintiffs' long-established state cause of action is set even higher here, because federal law itself provides no remedy for persons injured by inadequately labeled drugs. As this Court has repeatedly noted, it is "'difficult to believe that Congress would, without comment, remove all means of judicial recourse for those injured by illegal conduct.'" *Lohr*, 518 U.S. at 487 (quoting *Silkwood v. Kerr-McGee Corp.*, 464 U.S. 238, 251 (1984)); *see also Bates v. Dow AgroSciences LLC*, 544 U.S. 431, 449 (2005) ("If Congress had intended to deprive injured parties of a long available form of compensation, it surely would have expressed that intent more clearly.").

Moreover, in light of *Levine*, a ruling that Plaintiffs' claims are preempted would create an

arbitrary and irrational distinction between classes of patients: those whose prescriptions were filled with brand-name products would retain their right to sue, while those whose pharmacies substituted generic drugs would lose that right. There is certainly no evidence that Congress intended to draw this arbitrary distinction when it enacted the Hatch-Waxman Amendments.

To the contrary, as this Court observed in *Levine*, when Congress enacted the FDCA, "it determined that widely available state rights of action provided appropriate relief for injured consumers. It may also have recognized that state law remedies further consumer protection by motivating manufacturers to produce safe and effective drugs and to give adequate warnings." 129 S. Ct. at 1199-1200. Defendants offer the Court no reason to believe that Congress reached a different determination when it amended the FDCA by enacting the Hatch-Waxman Amendments.

II. DEFENDANTS HAVE NOT ESTABLISHED THAT IT WAS IMPOSSIBLE TO COMPLY WITH BOTH FEDERAL AND STATE LAW.

"Impossibility pre-emption is a demanding defense." *Levine*, 129 S. Ct. at 1199. To prevail on it at this early procedural stage, Defendants would have to demonstrate, as a matter of law, that it would have been "impossible for [them] to comply with both state and federal law," no matter the factual circumstances. *Crosby v. Nat'l Foreign Trade Council*, 530 U.S. 363, 372 (2000); *Florida Lime & Avocado Growers, Inc., v. Paul*, 373 U.S. 132, 142-43 (1963) (state law is preempted "where compliance

with both federal and state regulations is a physical impossibility").

Defendants have not made this showing. As discussed in Part II.A., Defendants now concede that they could have asked FDA to approve stronger warnings for both Reglan and generic metoclopramide and they could have asked the agency to issue a DHCP letter warning of the risks of long-term use, but they did not do either. And as discussed in Part II.B., Defendants have not even attempted to show that FDA would have rejected such proposed warnings, which is their burden under the affirmative defense of impossibility preemption.

A. There Is No Dispute that Defendants Could Have Sought FDA Approval for New Warnings, But Did Not Do So.

1. Defendants concede that they could have asked FDA to approve a stronger warning or to send a DHCP letter.

In their brief to this Court, Defendants Pliva, Teva, and UDL for the first time "freely concede" that neither the Hatch-Waxman Amendments nor FDA regulations prohibited them from asking FDA to approve stronger warnings for both Reglan and generic metoclopramide about the risk of tardive dyskinesia. Pliva Br. 48. They likewise concede that, as both courts below held, J.A. 413, 553, they could have asked FDA to send a DHCP letter alerting prescribers to the dangers of long-term use of Reglan

or generic metoclopramide.[25] As discussed in Section II.B., *infra* pp. 36-46, those concessions are fatal to Defendants' impossibility preemption argument before this Court.

Moreover, in 1992, FDA advised that "if an ANDA holder believes that new safety information should be added, it should provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised." 57 Fed. Reg. at 17961 cmt. 40. Defendants were prohibited by federal law, as by state law, from selling their products with inadequate warnings. *Compare* 21 U.S.C. § 352(f)(2) (App. 1a) (defining drugs without adequate warnings as misbranded); 21 U.S.C. § 331 (prohibiting sale of misbranded drug; *and* 21 C.F.R. § 201.57 (further explaining that drug "labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug") *with McCormack v. Hankscraft Co.*, 154 N.W.2d 488, 496 (Minn. 1967) (manufacturer must provide a "a warning as to any dangers reasonably foreseeable in its [product's] intended use"); *Stahl v. Novartis Pharm. Corp.*, 283 F.3d 254, 264 (5th Cir. 2002) (under the Louisiana Products Liability Act, plaintiff must demonstrate "that the manufacturer

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[25] For its part, Defendant Actavis never disputes that it could have asked FDA to strengthen the warnings on both products. Indeed, in its petition, No. 09-1501, Actavis did not even challenge the Fifth Circuit's rulings that it could have applied for a stronger warning through a PAS or asked FDA to issue a DHCP letter. The question presented in that petition was limited to whether states are preempted "from requiring additional safety information on a generic product label where the brand has not changed its label?" Actavis Pet. for Writ of Cert. i.

failed to use reasonable care to provide an adequate warning about . . . a potentially damage-causing characteristic" of its product).

If Defendants had asked FDA to approve stronger warnings, as they should have and now concede they could have done, FDA would have treated such a request promptly and seriously. MAPP 5200.6, at 3 ("ANDAs with serious safety concerns" are assigned the highest priority). But, despite mounting evidence of the serious risk of tardive dyskinesia associated with long-term metoclopramide use, *see supra*, p. 9, the Defendants never brought this information to the agency, nor did they ask FDA to "determine whether the labeling for the generic and listed drugs should be revised." 57 Fed. Reg. at 17961 cmt. 40.

2. Defendants could also have utilized other procedures to warn of the risks of long-term metoclopramide use.

In addition to simply asking FDA to approve a stronger warning or to send a DHCP letter, the Defendants could have used a number of regulatory procedures to seek approval for revised labeling or to warn health care practitioners directly. These procedures include a prior approval supplement, a CBE supplement, a Citizen Petition, or issuance of a DHCP letter by the company itself. The Defendants did not employ any of these methods to warn of the risk of tardive dyskinesia associated with long-term use of metoclopramide.

The parties, the courts below, and the United States disagree about precisely which of these

procedures Defendants could have employed in this situation. In light of Defendants' concessions discussed in the previous section, any disagreement about the proper approach need not be resolved. Nevertheless, Plaintiffs here explain why each of these procedures was available.

1. Defendants could have sought FDA approval for stronger warnings by filing a PAS under 21 C.F.R. §§ 314.70(b) and 314.97 (making § 314.70 applicable to ANDA holders). Under the PAS process, a drug company submits an application for a change to an approved NDA or ANDA and must obtain FDA approval before implementing that change. Because FDA approval precedes implementation under the PAS process, this procedure would have allowed FDA to evaluate a strengthened warning for both Reglan and generic metoclopramide before any labeling change was introduced into use, thus satisfying any concern about "sameness." Both courts of appeals concluded that this procedure was available to Defendants. J.A. 412, 551-52.

Pliva (collectively Pliva, Teva, and UDL) argues that the PAS process could not be used to add or strengthen label warnings, because the PAS regulation, § 314.70(b), includes an exception for changes that can be made via the CBE provision, § 314.70(c), and the CBE provision refers to changes made "[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction." Pliva Br. 44-46. The United States does not assert that the PAS process was prohibited but does contend that it

was not "expressly available to petitioners" for the same reason. U.S. Amicus Br. 14-15.[26]

Both Pliva and the government are mistaken. Their reading depends on the false assumption that any change that can be made by CBE must be made by CBE, as opposed to PAS. The PAS regulation provides, in relevant part, that an "applicant shall submit a supplement, and obtain FDA approval of it, before making . . . [a]ny change in labeling, except one described in paragraphs (c)(2) or (d) of this section." 21 C.F.R. § 314.70(b) and (b)(3)(i). This does not *prohibit* manufacturers from seeking prior approval for a labeling change of the type described in (c)(2); it simply makes clear that the CBE provision is available as an alternative.

At the same time, the CBE provision is phrased permissively. It governs "[s]upplements for changes that *may* be made before FDA approval," including labeling changes to add or strengthen warnings. 21 C.F.R. § 314.70(c) (emphasis added). The regulation does not require the exclusive use of CBE; if it were intended to do so, it would refer to changes that "must" be made prior to FDA approval.

Taken together, the two provisions establish that any labeling change can be made through the PAS process, but that warning changes may also be implemented through the CBE process without waiting for FDA approval. The use of CBE rather than PAS for warning changes is permissive, not mandatory, and PAS remains available. *Cf.* J.A. 412-

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[26] For its part, Actavis does not contest the availability of the PAS process. This is consistent with the limited scope of its petition. *See supra*, n.25.

12 ("manufacturers are *required* to use the prior approval process for 'labeling changes' (with a few exceptions including permissive use of the CBE process for warning enhancements . . .)").[27]

2. The CBE process was also available to Defendants, as three courts of appeals, and numerous district courts, have held. J.A. 550-51; *Gaeta v. Perrigo Pharm. Co.*, No. 09-15001, 2011 WL 198420 (9th Cir. Jan. 24, 2011); *Foster v. Am. Home Prods. Corp.*, 29 F.3d 165, 170 (4th Cir. 1994).[28] As just discussed, the CBE provision refers explicitly to labeling changes to "add or strengthen a contraindication, warning, precaution, or adverse reaction." 21 C.F.R. § 314.70(c)(2)(i); *see also* 21 C.F.R. § 314.97 (making § 314.70 applicable to ANDA holders).

Defendants, and the United States, argue that the court decisions approving generic drug manufacturers' use of the CBE process cannot be squared with the requirement that generic manufacturers include in all ANDAs, including supplements, a statement that the proposed labeling is the same as that for the RLD. 21 C.F.R. § 314.94(a)(8)(iiiv). This argument ignores that some

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[27] This reading of the regulations is also consistent with the history of the CBE process, which was created to allow drug companies to implement new warnings swiftly without prior approval, in the interest of drug safety and the public health. 30 Fed. Reg. 993-94.

[28] *See* district court decisions cited, *supra*, n.1. The Eighth Circuit concluded that it did not need to decide this issue, given the availability of other procedures to strengthen warnings on both Reglan and generic metoclopramide with FDA approval. J.A. 412.

differences in labeling are in fact permitted by § 314.94(a)(8)(iv), and the permitted differences include "labeling revisions made to comply with current FDA labeling guidelines or other guidance." As FDA explained when it proposed this regulation, that exception encompasses differences in proposed labeling because "the [RLD] labeling does not reflect current agency labeling standards," such as where "important new information about the safe use of a drug product" requires a labeling change, "but the reference listed drug's labeling has not yet been updated to reflect this change." 54 Fed. Reg. 28872, 28884 (July 10, 1989).

That is precisely the situation here: important new safety information required a change to the labeling for both brand-name Reglan and generic metoclopramide, but the Reglan label had not yet been updated to reflect the needed change. Thus, under § 314.94(a)(8)(iv), the generic manufacturers were permitted a difference in labeling to provide new safety information about the true risk of long-term metoclopramide use.

Under the CBE process, the manufacturer must submit its supplement application to FDA at the same time it makes the change to its label to strengthen warnings. 21 C.F.R. § 314.70(c). The CBE process is, therefore, another way for a generic drug manufacturer to bring evidence of the need for a new warning to FDA's attention and initiate consideration of whether the labels for both the RLD and generic drugs should be changed. 57 Fed. Reg. at 17961. If FDA approves the CBE change, it will also require the same new warning on the RLD label, thereby preserving the principle of consistent labeling across all bioequivalent products. Use of the

CBE process would, of course, lead to a temporary difference in labeling, just as it does when the RLD holder makes a CBE change. Section 314.94(a)(8)(iv), just like the CBE process itself, reflects FDA's determination that such temporary differences are justified in the interest of drug safety.[29]

3. The Defendants could also have sought FDA approval for a change to the warnings on both the Reglan and generic metoclopramide labels through the Citizen Petition process. 21 C.F.R. § 10.30. Under that process, any "person" may file a petition with FDA asking the agency to take any "form of administrative action." 21 C.F.R. §§ 10.30(a) and (b)(3). The filing of a Citizen Petition triggers formal FDA consideration of the request within a specified period of time. 21 C.F.R. § 10.30(e).

The Citizen Petition process has often been used to request agency action concerning the safety of particular drugs and drug companies often file

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[29] Defendants and FDA also cite another regulation that permits, but does not require, FDA to withdraw approval of an ANDA where the labeling for the generic drug "is no longer consistent" with that for the RLD. 21 C.F.R. § 314.150(b)(10). As the *Demahy* court explained, this provision was adopted in order to empower FDA to compel a generic company to make a labeling change already made by the RLD, not to prevent a generic manufacturer from acting promptly to comply with its obligations under § 201.57 to add warnings of serious new risks. J.A. 539 (quoting 57 Fed. Reg. at 17970 cmt. 78). Moreover, as this Court said in *Levine*, "the very idea that the FDA would bring an enforcement action against a manufacturer for strengthening a warning pursuant to the CBE regulation is difficult to accept—neither Wyeth nor the United States has identified a case in which the FDA has done so." 129 S. Ct. at 1197.

Citizen Petitions with FDA. *See supra*, pp. 16-17. Defendants could have filed a Citizen Petition here.

4. Finally, Defendants could themselves have issued a DHCP letter. The courts below were incorrect that such unilateral action was unavailable, as the government acknowledges. U.S. Amicus Br. 17.[30] Nothing in FDA regulations prohibits generic drug companies from sending DHCP letters without prior FDA approval. *Id.*

Defendants still argue that they were prohibited from sending a DHCP letter, because such a letter is considered "labeling" under the FDCA and therefore subject to the "sameness" requirement. Pliva Br. 46-47; Actavis Br. 24-25. But this argument ignores the critical regulatory distinction between approved labeling and promotional labeling. *See supra*, p. 17. Approved labeling, such as a drug's package insert, is, as the name suggests, the labeling language approved as part of the NDA or ANDA, and is therefore subject to the "sameness" requirement in § 314.94.[31] By contrast, what FDA terms "promotional labeling," including product advertising and DHCP letters, is not subject to that requirement.

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[30] Both courts of appeals concluded that Defendants could only ask FDA to issue a DHCP letter, not issue one on their own. J.A. 413-14, 553. As FDA has now made clear, this conclusion was erroneous. The courts of appeals based their conclusion on a provision in the 2007 FDAAA to implement a specific new risk evaluation and mitigation strategy (REMS). *Id.* (citing 21 U.S.C. § 355-1(i)(2)). That provision does not apply to DHCP letters that are not part of a REMS and, in any event, has no relevance to the question whether Defendants could have sent a DHCP letter long before it was enacted.

[31] Except, as discussed above, for differences permitted under 21 C.F.R. § 314.94(a)(8)(iv).

Id., at (a)(8)(iv) (sameness requirement applies to "container label, package insert, and Medication Guide").

Promotional labeling is subject to requirements that it not be misbranded, 21 C.F.R. § 314.150(b)(3), and that it include a true statement of product risks, 21 C.F.R. § 201.100(d)(1). The United States speculates that such a DHCP letter might misleadingly imply that generic metoclopramide was not therapeutically equivalent to its RLD and therefore constitute misbranding. U.S. Amicus Br. 17-18. Especially at the motion to dismiss stage, the Court must assume that the Defendants could have drafted a letter that would not have implied any such therapeutic difference.

In any event, as the United States acknowledges, FDA regulations state the Defendants were not prohibited from issuing a DHCP letter without prior FDA approval. As with a CBE change, any agency review of such a letter would have occurred only after it had been issued [32]

* * * *

In sum, there were numerous procedures available to Defendants to warn Plaintiffs and their prescribers of the risks associated with long-term metoclopramide use, including two that Defendants themselves concede—and the United States agrees—they could have employed.

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[32] As this Court noted in *Levine*, because the FDCA "contemplates that federal juries will resolve most misbranding claims, FDA's belief that a drug is misbranded is not conclusive." 129 S. Ct. at 1197 (citing 21 U.S.C. §§ 331, 332, and 334(a)-(b)).

B. Defendants Have Not Even Attempted to Show that FDA Would Have Rejected a Stronger Warning, Which Remains Their Burden Under the Affirmative Defense of Impossibility Preemption.

Defendants, having conceded that they could have sought FDA approval for stronger warnings, must prove that FDA would have denied authorization for the new warnings to establish that it was impossible for them to comply with both state and federal law. *Levine*, 129 S. Ct. at 1198 ("absent clear evidence that FDA would not have approved a change to Phenergan's label, we will not conclude that it was impossible for Wyeth to comply with both federal and state requirements"); *see also Gade v. Nat'l Solid Wastes Mgmt. Ass'n*, 505 U.S. 88, 110 (1992) (Kennedy, J., concurring) (quoting *Rice v. Norman Williams Co.*, 458 U.S. 654, 659 (1982)) (a "hypothetical or potential conflict is insufficient to warrant . . . pre-emption"). Federal preemption is an affirmative defense upon which the defendants bear the burden of proof. *Brown v. Earthboard Sports USA, Inc.*, 481 F.3d 901, 912 (6th Cir. 2007) (internal citation omitted); *see Levine*, 129 S. Ct. at 1198 (placing burden on defendant to provide clear evidence of impossibility).

Such a showing would undoubtedly be difficult, if not impossible, for Defendants to make. Prior to the time that metoclopramide was first prescribed to Ms. Mensing and Ms. Demahy, there was already considerable evidence that the risk of tardive dyskinesia associated with long-term use was far greater than the labeling approved by FDA in 1985 suggested. *See supra*, p. 9. Moreover, FDA's

2009 decision to order that a Boxed Warning regarding the risk of tardive dyskinesia be added to the Reglan and metoclopramide labels is strong evidence that the agency would have approved a stronger warning earlier, had any manufacturer asked FDA for authorization to add one. And the agency's decision to issue a Medwatch Safety Alert and accompanying news release at the time that it ordered the Boxed Warning, is strong evidence that FDA would have issued a similar DHCP letter, if any manufacturer had asked the agency to do so. *See supra*, pp. 10-11.

In the courts below, Defendants did not even attempt to show that, as a matter of fact, FDA would have rejected a stronger warning if Defendants had proposed one. Instead, in both *Mensing* and *Demahy*, Defendants filed motions to dismiss, asserting impossibility preemption as a "purely legal issue of statutory interpretation." J.A. 403, 522. Essentially, Defendants argued that they were absolutely prohibited from even proposing a stronger warning, because of the requirement that their labels remain consistent with the Reglan label; they never before acknowledged the possibility that they could have asked FDA to consider stronger warnings. Both courts of appeals properly rejected Defendants' extreme position, as has the United States. U.S. Amicus Br. 15-16.

Defendants have now abandoned the argument that the Hatch-Waxman Amendments prohibited them from even asking FDA to consider stronger warnings, "freely conceding" before this Court that they could have gone to FDA with information supporting a stronger warning and asked the agency to take action. The obvious

implication of this concession is that it converts the impossibility preemption inquiry into a question of fact—what would FDA have done in response to such a request?—that is inappropriate for resolution on a motion to dismiss.

Apparently recognizing this dilemma, Defendants have attempted to invert the preemption inquiry and shift the burden to Plaintiffs to prove that FDA would have approved a request for stronger warnings. They do this by mischaracterizing Plaintiffs' claims. Plucking a phrase out of context from the Eighth Circuit's decision, Defendants contend that Plaintiffs' claims are not traditional state-law inadequate warning claims at all, but rather claims that state law required generic manufacturers of metoclopramide to "take steps" to seek FDA approval for stronger warnings. Pliva Br. 49-50; Actavis Br. 16-17. And, they argue that to prove this hypothetical "take steps" claim, Plaintiffs bear the burden of showing that FDA would have approved a stronger warning in order to establish that their failure to "take steps" was the "cause" of Plaintiffs' injuries. Pliva Br. 53; Actavis Br. 17.[33] This proposition is wrong. Plaintiffs assert traditional, black-letter products liability claims under Minnesota and Louisiana law for injuries caused by a product sold with inadequate warnings[34]

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[33] Defendants' "take steps" argument depends on the assumption that they could not have provided adequate warnings of metoclopramide's risks without prior FDA approval. For this reason, if the Court agrees with Plaintiffs that Defendants could have made a CBE change or sent a DHCP letter, *supra*, pp. 31-33, 35-36, then Defendants' entire argument on this point would become moot.

[34] It is clear, in context, that the Eighth Circuit did not think it was adjudicating a "taking steps" claim. The first time

and such claims do not require Plaintiffs to prove that FDA would have approved a stronger warning. The only causation Plaintiffs must demonstrate is that the absence of an adequate warning caused their injuries.[35]

Moreover, although Defendants claim to find support for their theory in this Court's decision in *Levine*, nothing in *Levine* prevents Plaintiffs from bringing traditional inadequate warning claims in this situation or shifts the burden of proof to Plaintiffs. Instead, *Levine* explicitly recognized that the burden of proving impossibility remains on Defendants. 129 S. Ct. at 1198.

1. Proof regarding whether FDA would have approved a stronger warning is not an element of Plaintiff's cause of

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the court of appeals used that phrase, it was referring to federal regulatory requirements, not the elements of Ms. Mensing's cause of action. J.A. 410 ("The regulatory framework makes clear that a generic manufacturer must take steps to warn its customers when it learns it may be marketing an unsafe drug.") When the court returned to that phrase at the end of its impossibility preemption discussion, it was not a description of Plaintiff's claim, but rather part of a shorthand description of its reasons for rejecting the generic drug companies' preemption defense.

[35] Plaintiffs do not argue that whether FDA would have approved a stronger warning had one been requested is irrelevant. It is relevant to the preemption inquiry, but it is an issue on which the Defendants bear the burden of proof. *Levine*, 129 S. Ct. at 1198 ("absent clear evidence that the FDA would not have approved a change to Phenergan's label, we will not conclude that it was impossible for Wyeth to comply with both federal and state requirements. Wyeth has offered no such evidence.").

action under Minnesota or Louisiana law, but rather of Defendants' affirmative defense.

The principal causes of action asserted by both Ms. Mensing and Ms. Demahy in these cases are traditional products liability claims for inadequate warnings. J.A. 106-13 (strict liability); 115-21 (negligence); 143-45 (implied warranty); J.A. 442-45 (La. Prods. Liab. Act).[36] To establish causation for this type of claim, a plaintiff must show that the absence of adequate warnings caused her injuries. That is the *only* causation element of an inadequate-warning claim. *See, e.g., Restatement (Third) of Torts: Products Liability* § 6 (1998);[37] David G. Owen,

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[36] Ms. Mensing also asserts claims for misrepresentation by omission, negligent misrepresentation, fraud by concealment, constructive fraud, infliction of emotional distress, and violation of the Minnesota Consumer Protection Act. J.A. 122-49. Ms. Demahy also asserts a claim under the Louisiana Unfair Trade Practices and Consumer Protection Law. J.A. 445-47.

[37] Section 6 of the *Third Restatement* provides, in relevant part:

> (a) A manufacturer of a prescription drug . . . who sells . . . a defective drug . . . is subject to liability for harm to persons caused by the defect.
>
> (b) For purposes of liability under Subsection (a), a prescription drug . . . is defective if . . . the drug . . .
>
> (3) is not reasonably safe due to inadequate warnings as defined in Subsection (d)
>
> (d) A prescription drug . . . is not reasonably safe due to inadequate . . . warnings if

Products Liability Law § 9.1 (2d ed. 2008) ("If a user or consumer is injured as a result of a warning defect, because such danger or safety information was not provided, the manufacturer is subject to liability for the harm."); *id.* at § 11.4 ("the plaintiff must prove that the absence of that safety information caused the plaintiff's injury"); *see also* Pliva Br. 51 (in a "typical failure-to-warn case" plaintiff "needs to show only that (a) the drug is responsible for his or her injuries and (b) the existing warning's alleged inadequacy proximately caused the drug use that precipitated those injuries").

Minnesota and Louisiana follow these black-letter principles regarding proof of causation in an inadequate warning claim. The critical link for purposes of causation is that the drug's inadequate warnings cause the plaintiff's injury. Michael K. Steenson, *Minnesota Practice Series: Products Liability Law* § 4.11 (2006);[38] Louisiana Products

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> reasonable . . . warnings regarding foreseeable risks of hare are not provided to:
>
> (1) prescribing and other health-care providers who are in a position to reduce the risks of harm in accordance with the . . . warnings . . . .

[38] Consistent with this principle, the standard Minnesota special verdict form in an inadequate warning case asks the jury to answer only two questions: 1) "Was the product in a defective condition unreasonably dangerous to (the user) because (defendant manufacturer) failed to provide adequate (warnings) for the safe use of the product?" and 2) "Was the defective condition a direct cause of the (injuries) sustained by the plaintiff?" *Minnesota Jury Instructions Guides–Civil*, Special Verdict Form 75.90.

Liability Act (LPLA), La. Stat. Ann. §§ 2800.54.A., B.(3), & D. Proof that FDA would have rejected a stronger warning is an essential element of a manufacturer's preemption defense; proof that FDA would have approved the warning is not an element of the plaintiff's affirmative case.

Thus, in either state, to make out a prima facie case, Ms. Mensing or Ms. Demahy must prove that the absence of adequate warnings about the risks of long-term metoclopramide use was the cause of her injuries. But it is left to Defendants to try to prove that FDA would not have permitted stronger warnings at that time, as an element of their impossibility preemption affirmative defense.

Even if Defendants were correct that federal law required them to obtain FDA approval before changing their warnings, they offer no explanation why this would change the elements of Plaintiffs' causes of action under state law. Plaintiffs' claims remain traditional inadequate-warning claims, not the hypothetical "take steps" claims imagined by Defendants.[39]

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[39] Pliva repeatedly cites the brief filed by the United States in *Warner-Lambert Co. v. Kent*, 552 U.S. 440 (2008), as support for its "take steps" argument. Pliva Br. 5, 29, 56. But unlike Minnesota and Louisiana law, the Michigan statute at issue in *Kent* did require a plaintiff to prove how FDA would have acted in a hypothetical situation. Mich. Comp. Laws § 2946(5)(b) (requiring proof that FDA would not have approved a drug if the manufacturer had submitted all required information to overcome a statutory FDA-approval affirmative defense). The facts here are entirely different, which is why the United States opposes preemption in this case.

2. *Wyeth v. Levine* does not support Defendants' effort to shift the burden of proof to the Plaintiffs.

Wyeth v. Levine squarely placed the burden of proof on the defendant drug manufacturer to offer "clear evidence" that FDA "would not have approved" a warning change in order to establish its impossibility preemption affirmative defense. 129 S. Ct. at 1198. Defendants nevertheless argue that this Court's decision in *Levine* somehow shifts the burden to Plaintiffs in this case to prove that FDA would have approved a request for stronger warnings, in order to defeat their preemption defense. Defendants claim to find this requirement in this Court's discussion of the CBE process in *Levine*, Pliva Br. 52; Actavis Br. 25-26, but their argument rests on a "fundamental misunderstanding" of that ruling. 129 S. Ct. at 1197.

The central issue in *Levine* was whether a drug manufacturer or FDA "bears primary responsibility for drug labeling." 129 S. Ct. at 1197. This Court answered decisively that the responsibility rests with the manufacturer: "[T]hrough many amendments to the FDCA and to FDA regulations, it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times." *Id.* at 1197-98 (citing 21 C.F.R. § 201.80(e)).[40]

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[40] 21 C.F.R. § 201.80(e) is the same regulation as 21 C.F.R. § 201.57(e), as redesignated in 2006. *See supra*, n.17.

That core holding in *Levine* applies with full force to the manufacturers of generic drugs and weighs heavily against preemption in this case.

The Defendants ignore that holding and argue that *Levine* turned on the availability of a single procedure, CBE. But *Levine* focused on CBE, not because that particular procedure is necessary to avoid preemption, but rather because the trial judge had instructed the jury, without objection from Wyeth, that FDA regulations permitted a drug manufacturer to change its product label through that process. *Id.* at 1192-92. There was no reason for the Court to consider any other procedure because Wyeth conceded that CBE was an appropriate way to add or strengthen a label warning.[41]

Moreover, in light of the broad language this Court used in *Levine* in rejecting federal preemption under the FDCA, it makes no sense to read that decision as turning on the fact that CBE proposals may be implemented prior to formal FDA approval. As this Court recognized, even under the CBE process "the FDA retains authority to reject labeling changes . . . in its review of the manufacturer's supplemental application, just as it retains such authority in reviewing all supplemental applications." 129 S. Ct. at 1198.

In other words, there is no meaningful difference between the CBE process and the other procedures discussed above. Under any procedure, a manufacturer's proposed warning change is subject

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[41] Wyeth did argue that there was insufficient new evidence of Phenergan's risks to justify a CBE change and that FDA would have denied approval, but the Court rejected those arguments. *Id.* at 1196-97.

to FDA approval; therefore, as this Court recognized, the preemption inquiry turns on whether FDA would have denied approval of the change at the relevant time, and the burden of proof on that point belongs to Defendants. The Court gave no indication that it matters whether that FDA review follows, rather than precedes, implementation. To the contrary, the Court said that the defendant's focus on the terms of the CBE regulation reflected a "more fundamental misunderstanding" of the central issue in that case, which was the manufacturer's primary responsibility for the content of its label. *Id.* at 1197-98.

* * * *

Defendants concede that they could have asked FDA to approve stronger warnings for both Reglan and generic metoclopramide or to issue a DHCP letter warning of the risks of long-term metoclopramide use. And Defendants have not even attempted to establish that FDA would have denied such requests. It was therefore not impossible, as a matter of law, for Defendants to comply with their duties under both state and federal law, and their argument for impossibility preemption must be rejected.

III. STATE-LAW LIABILITY FOR FAILURE TO WARN WOULD NOT OBSTRUCT THE PURPOSES AND OBJECTIVES OF FEDERAL REGULATION OF GENERIC DRUGS

In the courts below, Defendants argued not only that it was impossible for them to comply with both federal and state law, but also that state tort liability would obstruct Congress's purposes and objectives in enacting the Hatch-Waxman

Amendments. In their briefs to this Court, Defendants appear to have largely abandoned this argument. Nevertheless, because their *amici* press this frustration-of-purpose argument, Plaintiffs address it here.[42]

A. State Tort Remedies Complement Congressional Purposes and the Federal Regulatory Scheme.

In *Levine*, this Court considered and rejected the argument that state tort remedies obstruct the purposes of federal law. "Congress enacted the FDCA to bolster consumer protection against harmful products." 129 S. Ct. at 1199. Congress did not create a federal remedy for consumers injured by unsafe drugs, because it recognized that "widely available state rights of action provided appropriate relief for injured consumers" and "further[ed] consumer protection by motivating manufacturers to produce safe and effective drugs and to give adequate warnings." *Id.* at 1199-1200. "If Congress thought state-law suits posed an obstacle to its objectives, it surely would have enacted an express pre-emption provision at some point during the FDCA's history." *Id.* at 1200.

As this Court also recognized, "the FDA has limited resources to monitor the 11,000 drugs on the market." *Id.* at 1202. State tort law "complements FDA regulation" by "uncover[ing] unknown drug hazards and provid[ing] incentives for drug manufacturers to disclose safety risks promptly. [It] also serve[s] a distinct compensatory function that

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[42] *See* Apotex, Inc. Amicus Br. in Supp. of Pet'r 26-30; *see generally* GPhA Amicus Br. in Supp. of Pet'r 19-32.

may motivate injured persons to come forward with information." *Id.*

Both courts of appeals recognized that these policy considerations apply with full force to state-law inadequate warning claims against generic drug companies. J.A. 417-18, 562. They took note that Congress had not included an express preemption provision in the Hatch-Waxman Amendments, even though it had included such a provision in the Medical Device Amendments only eight years before. J.A. 407, 533. They rejected the Defendants' argument that the sole purpose of the Hatch-Waxman Amendments was to make lower-cost generic drugs more widely available; because the Hatch-Waxman Amendments were enacted as amendments to the FDCA, they had to be considered in conjunction with that statute's fundamental emphasis on drug safety. J.A. 416-17, 561.

The courts below also properly rejected Defendants' more specific argument that state tort liability would undermine the goal of low-cost generic drugs by requiring generic drug companies to conduct expensive clinical trials to develop the scientific evidence necessary to support a labeling change; both courts recognized that "reasonable evidence of an association of a serious hazard with a drug," 21 C.F.R. § 201.57(e), can be found in adverse event reports and in published literature on metoclopramide, as Plaintiffs alleged. J.A. 416-17, 558-59. And, as documented above, considerable evidence was available to Defendants well before the time that metoclopramide was first prescribed to Ms. Mensing and Ms. Demahy. *See supra*, p. 9.

For all these reasons, the United States is correct when it says that state-law duties to warn do not obstruct the purposes and objectives of federal law. U.S. Amicus Br. 20-22 ("That argument is wrong.").

B. Preemption of Claims Against Generic Manufacturers Would Interfere with Congressional Objectives.

Not only does state tort liability complement the federal regulatory scheme, but a decision in favor of preemption would significantly *interfere* with federal objectives. Most importantly, it would pose a threat to public health, by eliminating any incentive for generic drug companies to ensure that drug labeling accurately reflected the risks posed by those products. *Cf.* J.A. 557 (preemption would necessarily require the conclusion "that Congress intended the name brand drug manufacturer to bear the sole burden of coping with incipient risks, even when it has ceased manufacturing the drug and left the market to generics").

"Adverse drug reactions (ADRs) are believed to be a leading cause of death in the United States." Lasser, *et al.*, *supra*, at 2215. Contrary to Defendants' assertions, many new drug risks do not emerge (or have not been addressed in labeling) until long after generic versions enter the market. *Id.* Indeed, almost a quarter century elapsed between the time the first generic metoclopramide entered the market and the time when a black-box warning about the risk of tardive dyskinesia was added to the label. Preemption would only increase the risk of such adverse drug events.

In so doing, preemption would also conflict with Congress's purpose of reducing health care costs. Each adverse drug event creates additional health care costs. In some cases, such as the Plaintiffs', these costs are substantial. If generic drug companies are not responsible for the costs that their negligence imposes on the health care system, those increased costs must be borne by the patients themselves, their insurers, and both state and federal governments through the Medicare and Medicaid programs.

A finding of preemption here would also undermine another central purpose of the Hatch-Waxman Amendments: to promote public confidence in the therapeutic equivalence of generic drugs and their RLDs. Once doctors, pharmacists, and patients understand that manufacturers of branded drugs are legally responsible for the adequacy of their warnings, but that manufacturers of generic drugs are not, they will each need to think twice about whether to substitute a generic drug for the RLD. Indeed, a ruling in favor of preemption might even lead state legislatures to rethink their support for generic drugs through their state substitution laws. And each time someone decides not to substitute a generic drug because of concerns about their therapeutic equivalence, that too will increase costs to the health care system. FDA, FY2011 Budget, *Protecting Patient Safety*, at 410 (2011) (cost savings from generic substitution depend on "the public's confidence in the safety, quality, and comparability of generic drugs to their brand equivalents").[43]

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[43] *Available at* http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/BudgetReports/UCM205622.pdf.

A ruling in favor of preemption would also leave persons injured by inadequately labeled prescription drugs without remedy for their injuries. That would frustrate Congress's purpose of preserving state law remedies that protect injured consumers and complement the federal regulatory scheme.[44]

During hearings on the Hatch-Waxman Amendments, concerns were raised about whether generic drugs would really be as safe as branded

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[44] Defendant Actavis argues that any lack of legal remedy is not the result of Defendants' preemption arguments, but rather was caused by the Plaintiffs' "strategic decision" not to sue their physicians for malpractice for prescribing metoclopramide for more than the approved twelve weeks. Actavis Br. 26 n.14. However, "off-label prescribing is an accepted form of medical practice, as FDA has long acknowledged:

> Congress did not intend FDA to interfere with the practice of medicine. . . . A physician may prescribe a drug for uses or in treatment regimens or patient populations that are not listed on the FDA-approved labeling. . . . Under certain circumstances, off-label uses of approved products are appropriate, rational, and accepted medical practice.

Unapproved Uses of Prescription Drugs, Before the S. Comm. on Labor and Human Resources, 104th Cong. (Feb. 22, 1996) (testimony of William B. Schultz, Deputy Commissioner for Policy, FDA).

Estimates are that close to half of all drug prescriptions are written for indications that have not been approved by FDA. Kaspar J. Stoffelmayr, *Products Liability and "Off-Label" Uses of Prescription Drugs*, 63 U. Chi. L. Rev. 275, 278 (1996). Actavis does not explain how the Plaintiffs' physicians could be held liable for prescribing metoclopramide long-term when it failed to warn them of the serious risks associated with this practice.

drugs. Representatives of the generic drug industry repeatedly assured Congress that they would be, that generic drug companies were responsible manufacturers with large research departments, capable of reviewing adverse reactions and keeping up with the scientific literature, and that they would do whatever was necessary "to provide for the safety and well-being of those that are using the drug."[45] Congress relied on these representations of corporate responsibility when it enacted the Hatch-Waxman Amendments. This Court should not allow Defendants to disclaim those responsibilities now.

IV. THE PLAINTIFFS' CLAIMS ARE NOT PREEMPTED UNDER *ARKANSAS LOUISANA GAS CO. V. HALL* OR *BUCKMAN V. PLAINTIFFS' LEGAL COMMITTEE*

Apparently recognizing that Defendants cannot meet their burden of proving that Plaintiffs' traditional state-law inadequate warning claims are preempted on the basis of either impossibility or frustration of purpose, Pliva offers two final arguments. Both are premised on Defendants' false

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[45] *Drug Legislation: Hearings Before the Subcomm. on Health and the Environment of the H. Comm. on Energy and Commerce*, 98th Cong. 48 (July 25, 1983) (testimony of Kenneth N. Larsen, Chairman, Generic Pharmaceutical Industry Association and President, Zenith Laboratories, Inc.); *see also id.* at 45-47 (generic manufacturers "are sensitive to the importance of looking at adverse reactions" and "are expected to know . . . what the literature says"); *Id.* at 50 (testimony of William Haddad, Executive Officer and President, Generic Pharmaceutical Industry Association) (every generic drug company "has a large research staff" and "researches adverse reaction").

assertion, discussed earlier, that Plaintiffs' claims are not traditional state-law inadequate warning claims at all, but rather claims that state law required generic manufacturers of metoclopramide to "take steps" to seek FDA approval for stronger warnings. Pliva argues that such a "take steps" claim is preempted under *Arkansas Louisiana Gas Co. v. Hall*, 453 U.S. 571 (1981), because speculation about how FDA would have responded to a request for stronger warnings would "necessarily usurp the agency's authority," and is also preempted under *Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341 (2001), because it would "directly interfere with a federal regulatory regime." Pliva Br. 49. Actavis does not join in these arguments in its brief.

The short answer to these arguments, as discussed above, is that Plaintiffs' claims are not some sort of unprecedented new "taking steps" claim, but rather traditional, black-letter products liability claims under Minnesota and Louisiana law for injuries caused by a product sold with inadequate warnings.

A. *ArkLa Gas* Is Inapplicable Because "Congress Did Not Intend FDA Oversight to be the Exclusive Means of Ensuring Drug Safety and Effectiveness."

Starting from the false premise that Plaintiffs' claims are "taking steps" claims, Pliva argues that these claims are barred by *ArkLa Gas*, a case involving the federal "filed rate doctrine" under the Natural Gas Act. In *ArkLa Gas*, this Court held that a state-law breach of contract action for damages based on a contractual purchase price for natural gas

that differed from the rate that had been filed with and approved by the Federal Power Commission (FPC) was preempted by the filed rate doctrine. 453 U.S. at 584-85.

Pliva describes *ArkLa Gas* as standing for the sweeping proposition that any claim that depends on "speculation about what a federal agency would have done in hypothetical proceedings" is preempted because "the trial of such state-law claims unavoidably usurps the federal agency's exclusive authority." Pliva Br. 53. But that is a dramatic overstatement of the holding in *ArkLa Gas*, which was a narrow holding about the authority of the FPC. Indeed, this Court has never even cited *ArkLa Gas* outside the context of the filed rate doctrine.

Under the Natural Gas Act, Congress had granted the FPC exclusive authority to decide whether rates for natural gas were "just and reasonable," and the definition of a "just and reasonable" rate was one that had been filed with and approved by the Commission. 453 U.S. at 577 ("The authority to decide whether the rates are reasonable is vested by § 4 of the Act solely in the Commission, and the right to a reasonable rate is the right to the rate which the Commission files or fixes.") (internal citations and quotations omitted). Because Congress had "established an exclusive form of regulation," state courts were precluded from awarding contract damages that departed from the approved filed rate. *Id.* at 580.

Here, by contrast, "Congress did not intend FDA oversight to be the exclusive means of ensuring drug safety and effectiveness." *Levine*, 129 S. Ct. at 1200. Congress and FDA both recognize that state

regulation of prescription drugs through the tort system complements and furthers the federal interest in drug safety. *See supra*, p. 47-48. For this reason, *ArkLa Gas* is wholly inapplicable to this case.

B. *Buckman* Does Not Apply to Plaintiffs' Inadequate Warning Claims, Which Long Pre-date the Hatch-Waxman Amendments and Which Congress Contemplated Would be Part of the Regulatory Scheme.

Finally, Pliva argues that Plaintiffs' claims are preempted by this Court's holding in *Buckman*. But this argument too depends on Pliva's mischaracterization of Plaintiffs' claims as some sort of novel "take steps" claim, because *Buckman* has no application to traditional state causes of action such as Plaintiffs here assert.

In *Buckman*, this Court held that a state-law "fraud-on-the-FDA" claim was preempted, because such a claim would interfere with the "delicate balance of statutory objectives" that FDA must try to achieve in deciding whether and how to police fraud against the agency. 531 U.S. at 348. Central to the Court's holding was its recognition that "[p]olicing fraud against federal agencies is hardly 'a field which the States have traditionally occupied,'" *id.* at 347 (quoting *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218, 230 (1947)), and therefore the presumption against preemption did not apply. *Id.* at 348. The Court was also concerned that state court policing of fraud on the agency would cause applicants to "deluge" FDA with information, which would interfere with fulfillment of its regulatory duties, *id.*

at 351, the specific concern that Pliva reiterates here. Pliva Br. 59-61.

Buckman is not relevant here because, unlike the fraud-on-the-agency claim at issue there, this case involves traditional state law causes of action; in light of "the historic primacy of state regulation of matters of health and safety," *Lohr*, 518 U.S. at 485, the presumption against preemption is fully applicable. *Levine*, 129 S. Ct. at 1195-96. The *Buckman* court expressly distinguished that case from cases involving a "traditional state tort law principles of [a manufacturer's] duty of care," 531 U.S. at 352 (distinguishing both *Silkwood* and *Lohr* on this basis), and, in *Levine*, this Court distinguished the claim at issue in *Buckman* from failure-to-warn claims against drug manufacturers on the same basis. 129 S. Ct. at 1195 n.3.

This Court found that the claim at issue in *Buckman* might skew the "delicate balance of statutory objectives" FDA seeks to achieve in deciding when and how best to punish and deter fraud. 531 U.S. at 348. By contrast, Plaintiffs' claims here complement federal drug regulation by providing "incentives for drug manufacturers to disclose safety risks promptly." *Levine*, 129 S. Ct. at 1202. Moreover, unlike a "fraud-on-the-FDA" claim, traditional failure-to-warn claims long "predated the federal enactments in question," and thus, it must be assumed, were a part of the regulatory scheme contemplated by Congress when it enacted the Hatch-Waxman Amendments. *Buckman*, 531 U.S. at 353; *see also South Dakota v. Yankton Sioux Tribe*, 522 U.S. 329, 351 (1998) ("Congress is aware of existing law when it passes legislation.") (internal citation and quotation marks omitted).

There is also no reason why a ruling in favor of Plaintiffs should lead to a deluge of submissions to FDA. The duty to revise warning labels arises only when "there is reasonable evidence of an association of a serious hazard with a drug," 21 C.F.R. § 201.57(e), not every time "a single adverse event report" is received. Pliva Br. 60. Plus, generic drug companies already have a duty to submit all adverse event reports to the agency and to provide FDA with an annual summary of significant new information that might affect the safety, effectiveness, or labeling of their product. 21 C.F.R. §§ 314.98(a) and (c). If they are already fulfilling those duties, there should be little left to submit.

The same "deluge" argument was made in *Levine*,[46] and this Court implicitly rejected that argument when it found no conflict preemption in that case. Nor did the *Levine* decision itself trigger a flood of labeling supplement submissions to the agency; FDA reports that supplement applications have actually fallen since that decision.[47]

---

[46] PhRMA & BIO Amicus Br. in Supp. of Pet'r, at 36-38, *Wyeth v. Levine*, 129 S. Ct. 1187 (2009) (No. 06-1249).

[47] *See* FDA, Dep't of Health & Human Servs., *FY 2010 Performance Report to the President and Congress for the Prescription Drug User Fee Act*, at 26 (2010) (table showing that for fiscal year 2010, the first full fiscal year after *Levine* was decided, both the number of supplements not requiring prior agency approval (*i.e.*, CBE supplements) and the total number of manufacturing supplements filed with the agency dropped to its lowest level in five years), *available at* http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/PDUFA/ucm243357.htm. Nor is there any evidence that *Levine* prompted a flood of failure-to-warn litigation. *See* Office of Judges Programs, Admin. Office of the U.S. Courts, *Fed. Judicial Caseload*

In short, neither *ArkLa Gas* nor *Buckman* supports Pliva's argument that Plaintiffs' traditional state-law inadequate warning claims are preempted.

CONCLUSION

The judgments of the Fifth and Eighth Circuit Courts of Appeals should be affirmed.

February 23, 2011 Respectfully submitted,

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Statistics, at 46 (March 2010) (Table C-2, showing that excluding airline-, marine-, motor vehicle- and asbestos-specific cases, fewer "Personal Injury/Product Liability" cases were commenced in federal court during the 12 months prior to March 31, 2010 than during the previous year), *available at* http://www.uscourts.gov/Statistics/FederalJudicialCaseloadStatistics/FederalJudicialCaseloadStatistics2010.aspx.

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APPENDIX

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UNITED STATES CODE

TITLE 21. FOOD AND DRUGS

CHAPTER 9. FEDERAL FOOD, DRUG, AND

COSMETIC ACT

SUBCHAPTER V. DRUGS AND DEVICES

PART A. DRUGS AND DEVICES

§ 352. Misbranded drugs and devices

A drug or device shall be deemed to be misbranded—

* * *

(f) Directions for use and warnings on label

Unless its labeling bears (1) adequate directions for use; and (2) such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users.

* * *

APPENDIX B:

21 C.F.R. § 10.30 (2001) - (excerpt)

CODE OF FEDERAL REGULATIONS

TITLE 21. FOOD AND DRUGS

CHAPTER I. FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

SUBCHAPTER A. GENERAL

PART 10. ADMINISTRATIVE PRACTICES AND PROCEDURES

SUBPART B. GENERAL ADMINISTRATIVE PROCEDURES

§ 10.30 Citizen petition.

(a) This section applies to any petition submitted by a person (including a person who is not a citizen of the United States) except to the extent that other sections of this chapter apply different requirements to a particular matter.

(b) A petition (including any attachments) must be submitted in accordance with § 10.20 and in the following form:

* * *

Citizen Petition

The undersigned submits this petition under ——— (relevant statutory sections, if known) of the ——— (Federal Food, Drug, and Cosmetic Act or the Public Health Service Act or any other statutory provision for which authority has been delegated to the Commissioner of Food and Drugs under 21 CFR 5.10) to request the Commissioner of Food and Drugs to ——— (issue, amend, or revoke a regulation or order or take or refrain from taking any other form of administrative action).

A. Action requested

((1) If the petition requests the Commissioner to issue, amend, or revoke a regulation, the exact wording of the existing regulation (if any) and the proposed regulation or amendment requested.)

((2) If the petition requests the Commissioner to issue, amend, or revoke an order, a copy of the exact wording of the citation to the existing order (if any) and the exact wording requested for the proposed order.)

((3) If the petition requests the Commissioner to take or refrain from taking any other form of administrative action, the specific action or relief requested.)

B. Statement of grounds

(A full statement, in a well organized format, of the factual and legal grounds on which the petitioner relies, including all relevant information and views on which the petitioner relies, as well as

representative information known to the petitioner which is unfavorable to the petitioner's position.)

* * *

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

* * *

(c) A petition which appears to meet the requirements of paragraph (b) of this section and § 10.20 will be filed by the Dockets Management Branch, stamped with the date of filing, and assigned a docket number.

* * *

(d) An interested person may submit written comments to the Dockets Management Branch on a filed petition, which comments become part of the docket file.

* * *

(e)(1) The Commissioner shall, in accordance with paragraph (e)(2), rule upon each petition filed under paragraph (c) of this section, taking into consideration (i) available agency resources for the category of subject matter, (ii) the priority assigned to the petition considering both the category of subject matter involved and the overall work of the agency, and (iii) time requirements established by statute.

* * *

APPENDIX C:

21 C.F.R. § 200.5 (2001) – (excerpt)

CODE OF FEDERAL REGULATIONS

TITLE 21. FOOD AND DRUGS

CHAPTER I. FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

SUBCHAPTER C. DRUGS: GENERAL

PART 200. GENERAL

SUBPART A. GENERAL PROVISIONS

§ 200.5 Mailing of important information about drugs.

Manufacturers and distributors of drugs and the Food and Drug Administration occasionally are required to mail important information about drugs to physicians and others responsible for patient care. In the public interest, such mail should be distinctive in appearance so that it will be promptly recognized and read. The Food and Drug Administration will make such mailings in accordance with the specifications set forth in this section. Manufacturers and distributors of drugs are asked to make such mailings as prescribed by this section and not to use the distinctive envelopes for ordinary mail.

* * *

APPENDIX D:

21 C.F.R. § 201.57(c) (2001) – (excerpt)

CODE OF FEDERAL REGULATIONS

TITLE 21. FOOD AND DRUGS

CHAPTER I. FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

SUBCHAPTER C. DRUGS: GENERAL

PART 201. LABELING

SUBPART B. LABELING REQUIREMENTS FOR PRESCRIPTION DRUGS AND/OR INSULIN

§ 201.57 Specific requirements on content and format of labeling for human prescription drugs.

Each section heading listed in § 201.56(d), if not omitted under § 201.56(d)(3), shall contain the following information in the following order:

• • •

(c) "Warnings": Under this section heading, the labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved. A specific warning relating to a use not provided for under the

"Indications and Usage" section of the labeling may be required by the Food and Drug Administration if the drug is commonly prescribed for a disease or condition, and there is lack of substantial evidence of effectiveness for that disease or condition, and such usage is associated with serious risk or hazard. Special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box.

* * *

APPENDIX E:

21 C.F.R. § 314.70 (2001) – (excerpt)

CODE OF FEDERAL REGULATIONS

TITLE 21. FOOD AND DRUGS

CHAPTER I. FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

SUBCHAPTER D. DRUGS FOR HUMAN USE

PART 314. APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

SUBPART B. APPLICATIONS

§ 314.70 Supplements and other changes to an approved application.

(a) Changes to an approved application. The applicant shall notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application. The notice is required to describe the change fully. Depending on the type of change, the applicant shall notify FDA about it in a supplemental application under paragraph (b) or (c) of this section or by inclusion of the information in the annual report to the application under paragraph (d) of this section.

* * *

(b) Supplements requiring FDA approval before the change is made. An applicant shall submit a supplement, and obtain FDA approval of it, before making the changes listed below in the conditions in an approved application, unless the change is made to comply with an official compendium.

* * *

(3) Labeling.

(i) Any change in labeling, except one described in paragraphs (c)(2) or (d) of this section.

* * *

(c) Supplements for changes that may be made before FDA approval. An applicant shall submit a supplement at the time the applicant makes any kind of change listed below in the conditions in an approved application, unless the change is made to comply with an official compendium.

* * *

(2) Changes labeling to accomplish any of the following:

(i) To add or strengthen a contraindication, warning, precaution, or adverse reaction;

(ii) To add or strengthen a statement about drug abuse, dependence, or overdosage; or

(iii) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the product.

(iv) To delete false, misleading, or unsupported

indications for use or claims for effectiveness.

* * *

APPENDIX F:

21 C.F.R. § 314.80(b) and (c) (2001) – (excerpt)

CODE OF FEDERAL REGULATIONS

TITLE 21. FOOD AND DRUGS

CHAPTER I. FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

SUBCHAPTER D. DRUGS FOR HUMAN USE

PART 314. APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

SUBPART B. APPLICATIONS

§ 314.80 Postmarketing reporting of adverse drug experiences.

* * *

(b) Review of adverse drug experiences. Each applicant having an approved application under § 314.50 or, in the case of a 505(b)(2) application, an effective approved application, shall promptly review all adverse drug experience information obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers.

* * *

(c) Reporting requirements. The applicant shall report to FDA adverse drug experience information, as described in this section.

* * *

(1)(i) Postmarketing 15-day "Alert reports". The applicant shall report each adverse drug experience that is both serious and unexpected, whether foreign or domestic, as soon as possible but in no case later than 15 calendar days of initial receipt of the information by the applicant.

* * *

(2) Periodic adverse drug experience reports.

(i) The applicant shall report each adverse drug experience not reported under paragraph (c)(1)(i) of this section at quarterly intervals, for 3 years from the date of approval of the application, and then at annual intervals.

* * *

APPENDIX G:

21 C.F.R. § 314.81 (2001) – (excerpt)

CODE OF FEDERAL REGULATIONS

TITLE 21. FOOD AND DRUGS

CHAPTER I. FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

SUBCHAPTER D. DRUGS FOR HUMAN USE

PART 314. APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

SUBPART B. APPLICATIONS

§ 314.81 Other postmarketing reports.

(a) Applicability. Each applicant shall make the reports for each of its approved applications and abbreviated applications required under this section and section 505(k) of the act.

* * *

(b) Reporting requirements. The applicant shall submit to the Food and Drug Administration at the specified times two copies of the following reports:

* * *

(2) Annual report. The applicant shall submit each year within 60 days of the anniversary date of U.S. approval of the application, two copies of the report

to the FDA division responsible for reviewing the application . . . . The report is required to contain in the order listed:

(i) Summary. A brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product. The report is also required to contain a brief description of actions the applicant has taken or intends to take as a result of this new information, for example, submit a labeling supplement, add a warning to the labeling, or initiate a new study.

* * *

APPENDIX H:

21 C.F.R. § 314.94(a)(8)(iii) and (iv) (2001) – (excerpt)

CODE OF FEDERAL REGULATIONS

TITLE 21. FOOD AND DRUGS

CHAPTER I. FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

SUBCHAPTER D. DRUGS FOR HUMAN USE

PART 314. APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

SUBPART C. ABBREVIATED APPLICATIONS

§ 314.94 Content and format of an abbreviated application.

* * *

(a) Abbreviated new drug applications. Except as provided in paragraph (b) of this section, the applicant shall submit a complete archival copy of the abbreviated new drug application that includes the following:

* * *

(8) Labeling—

* * *

(iii) Statement on proposed labeling. A statement that the applicant's proposed labeling including, if applicable, any Medication Guide required under part 208 of this chapter is the same as the labeling of the reference listed drug except for differences annotated and explained under paragraph (a)(8)(iv) of this section.

(iv) Comparison of approved and proposed labeling. A side-by-side comparison of the applicant's proposed labeling including, if applicable, any Medication Guide required under part 208 of this chapter with the approved labeling for the reference listed drug with all differences annotated and explained. Labeling (including the container label, package insert, and, if applicable, Medication Guide) proposed for the drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers. Such differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act.

APPENDIX I:

21 C.F.R. § 314.97 (2001)

CODE OF FEDERAL REGULATIONS

TITLE 21. FOOD AND DRUGS

CHAPTER I. FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

SUBCHAPTER D. DRUGS FOR HUMAN USE

PART 314. APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

SUBPART C. ABBREVIATED APPLICATIONS

§ 314.97 Supplements and other changes to an approved abbreviated application.

The applicant shall comply with the requirements of §§ 314.70 and 314.71 regarding the submission of supplemental applications and other changes to an approved abbreviated application.

APPENDIX J:

21 C.F.R. § 314.98 (2001)

CODE OF FEDERAL REGULATIONS

TITLE 21. FOOD AND DRUGS

CHAPTER I. FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

SUBCHAPTER D. DRUGS FOR HUMAN USE

PART 314. APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

SUBPART C. ABBREVIATED APPLICATIONS

§ 314.98 Postmarketing reports.

(a) Except as provided in paragraph (b) of this section, each applicant having an approved abbreviated new drug application under § 314.94 that is effective shall comply with the requirements of § 314.80 regarding the reporting and recordkeeping of adverse drug experiences.

(b) Each applicant shall submit one copy of each report required under § 314.80 to the Division of Epidemiology and Surveillance (HFD-730), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

(c) Each applicant shall make the reports required under § 314.81 and section 505(k) of the act for each

of its approved abbreviated applications.

REPLY BRIEF

Supreme Court, U.S.
FILED
MAR 23 2011
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IN THE
Supreme Court of the United States

PLIVA, INC., ET AL.,
Petitioners,
v.
GLADYS MENSING,
Respondent.

ACTAVIS ELIZABETH LLC,
Petitioner,
v.
GLADYS MENSING,
Respondent.

ACTAVIS INC.,
Petitioner,
v.
JULIE DEMAHY,
Respondent.

On Writs of Certiorari to the United States Courts of Appeals for the Eighth Circuit and for the Fifth Circuit

REPLY BRIEF OF PETITIONERS ACTAVIS INC. AND ACTAVIS ELIZABETH LLC

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INTRODUCTION

Mensing and Demahy brought textbook failure-to-warn claims under Minnesota and Louisiana law. Each alleged that, prior to her injuries, the generic drug defendants had new information about the risks of metoclopramide, had a duty to warn physicians about these risks, should have issued new warnings, failed to do so, and proximately caused plaintiff's injuries. Although the United States has filed a brief supporting Mensing and Demahy, the government agrees with petitioners that "an ANDA holder may not unilaterally change its approved labeling." Brief for the United States as *Amicus Curiae* Supporting Respondents ("US Br.__") 16. Thus, the application of established conflict preemption principles to plaintiffs' direct failure-to-warn claims leads to one conclusion: plaintiffs' claims are preempted.

Perhaps realizing that their traditional direct failure-to-warn claims are preempted, respondents now advance a new theory that the generic manufacturers had a duty to warn respondents' physicians by the indirect means of notifying FDA, which then could have requested that the brand manufacturer add a new warning to the label, at which time a generic manufacturer could legally add a warning to its own label. While this novel theory has attracted much attention, particularly among the *amici*, it merely serves to distract from what should be the central focus of these proceedings: that the Court rule that the direct failure-to-warn claims that respondents actually pled are preempted. The *Demahy* decision held that generic drug

manufacturers can unilaterally change their labels under the Federal, Food, Drug and Cosmetic Act ("FFDCA") regulations, while the *Mensing* court declined to decide the issue. To date, one other Circuit and numerous district courts have incorrectly held that generic manufacturers may unilaterally amend their labels. It is imperative that the Court correct this misreading of the statute and regulations.

Preemption issues related to respondents' new failure-to-ask theory are not ready for review, and in any event, because the complaints do not allege a claim other than a direct failure-to-warn claim, they should be dismissed. State courts have not yet identified a state law basis for the new claims proposed by plaintiffs, defined the elements of any such claim, or considered where the burden of proof should lie. The Court should allow them to do so in the first instance, after a plaintiff has actually alleged such a claim.

The almost uniform, erroneous rulings by the lower courts as to whether a direct failure-to-warn claim against a generic manufacturer is preempted are due to a misreading of this Court's decision in *Wyeth v. Levine*, 129 S. Ct. 1187 (2009). But the lower courts are also misreading *Wyeth*'s statements regarding the burden of proof on whether FDA would have agreed to a label change where it would be an element of the plaintiff's claims. In fact, *Wyeth* has no application to the allocation of the burden of proof in such a situation, and the lower courts should be permitted to decide this question in a case where any

new legal claim that is permitted under state law is appropriately alleged and prosecuted.

I. Plaintiffs' Failure-to-Warn Claims Are Preempted.

A. Federal Law Prohibited a Generic Manufacturer From Adding a New Warning to Its Drug Label Until the Brand Manufacturer Had Changed Its Label.

As the United States demonstrates in its brief, plaintiffs' claims that the generic manufacturers may be held liable for not adding a warning to the metoclopramide label are preempted because the generic manufacturers could not independently have added a warning to the label of a generic drug without violating federal law. US Br. 15-17. This is also clear from the plain meaning of the FFDCA and FDA's regulations, and from the Agency's consistent and longstanding interpretation of the applicable statutory and regulatory provisions. Actavis Br. 18-24.

Plaintiffs claim that generic defendants could have changed their label through FDA's Changes Being Effected ("CBE") regulation, which permits a brand manufacturer to make changes to its label as soon as it submits a supplemental application to FDA. To support this argument, plaintiffs rely on *Wyeth*, where this Court held that "it has remained a central premise of federal drug regulation that the manufacturer [Wyeth] bears responsibility for the content of its label at all times," including both

"crafting an adequate label and . . . ensuring that its warnings remain adequate." 129 S. Ct. at 1197-98.

As this Court also pointed out, "prior to 2007, FDA lacked the authority to order manufacturers to revise their labels." *Id* at 1198. In other words, during the timeframe pertinent to this case, brand manufacturers had control over the label of their pharmaceutical products. In contrast to the law applicable to brands established in *Wyeth*, the Hatch-Waxman Act and FDA regulations require that the generic product have the same labeling as the brand. Actavis Br. 18-24. As a result, prior to 2007 brand drug manufacturers effectively controlled the labeling of generic drugs.

Thus FDA's regulations require that each abbreviated drug application, amendment and supplement contain "[a] statement that the applicant's proposed labeling . . . is the same as the labeling of the reference listed drug." 21 C.F.R. § 314.94(a)(8)(iii); *see* Actavis Br. 18-19, 21. The regulations are very clear that any change made in a supplement, pursuant to the CBE regulation or otherwise, is therefore subject to the same labeling requirement, *i.e.*, the labeling in the supplement must also mirror the brand label. Actavis Br. 19. FDA guidance also states that a generic manufacturer must "ensur[e] that the labeling contained in its application is the same as the currently approved labeling of the [brand]." *See* FDA, *Guidance for Industry, Revising ANDA Labeling Following Revision of the RLD Labeling* (May 2000); *see* Actavis Br. 21-22.

Apparently recognizing that the argument that they persuaded the Fifth Circuit to adopt in *Demahy* is fatally flawed, in this Court, respondents have advanced a new, and incorrect, rationale for the same outcome, namely that FDA's regulations, 21 C.F.R. § 314.94(a)(8)(iv), permit differences in generic labeling "to comply with current FDA labeling guidelines or other guidance." *See* Opp. Br. 33-34. To support this argument, respondents cite the preamble to that regulation in which FDA stated that the exception encompasses differences in proposed labeling because "important new information about the safe use of a drug product" requires a labeling change. Opp. Br. 34 (*quoting* 54 Fed. Reg. 28872, 28884 (July 10, 1989)).

Respondents' argument is inconsistent with statements FDA made when it issued the regulation and with statements that the United States has made on behalf of FDA to this Court. In the preamble to the regulations, FDA stated that the exception to same labeling applies when "for example, the agency *may require* a change in the labeling to make available important new information about the safe use of a drug product." Abbreviated New Drug Application Regulations, Proposed Rule, 54 Fed. Reg. 28872, 28884 (July 10, 1989) (emphasis added). As the United States notes, "[t]here was no such action on FDA's initiative in the period relevant to these cases." US Br. 16 n.7. Moreover, in the preamble to the final rule, in FDA's discussion of this exact provision, the Agency explicitly rejected a comment that sought a revision that would have permitted ANDA applicants to deviate from the labeling for the reference listed drug

to add contraindications, warnings and other safety related information. Abbreviated New Drug Application Regulations, Final Rule, 57 Fed. Reg. 17950, 17961 (April 28, 1992).

As explained above, the plain and only meaning of FDA's regulations is that at all times the labeling of generic drugs must be the same as the brand. If, however, there were any ambiguity in the Agency's regulations, which have the force of law, then the Agency's consistent and longstanding interpretation of those regulations would be entitled to deference. *See* Actavis Br. 22. Even if FDA had not repeatedly taken that position, its position in the legal briefs filed with this Court, which is consistent with the regulatory text, is, by itself, entitled to deference. *Chase Bank USA, N.A. v. McCoy*, 131 S. Ct. 871, 880-81 (2011).

B. Federal Law Prohibited a Generic Manufacturer From Sending New Warning Information to Physicians Until the Brand Manufacturer Had Changed Its Label.

The United States also correctly rejects plaintiffs' argument that the generic manufacturers could have issued a Dear Healthcare Professional (DHCP) letter with additional warnings. US Br. 18-19. FDA has defined DHCP letters as "correspondence . . . intended to alert . . . health care providers . . . about important new information regarding a human drug or biologic." FDA, *Guidance for Industry and FDA Staff: Dear Health Care Provider Letters: Improving Communication of*

Important Safety Information at 1 (Draft, November 2010). As the Fifth Circuit, the Eighth Circuit, *and* the United States all correctly have concluded, the generic drug manufacturers could not have lawfully included a warning in a DHCP letter that was different from the warning on the brand label. JA 553, 413; US Br. 18-19.

In their opposition, respondents incorrectly state that FDA has asserted (in the certiorari brief filed by the United States) that the Fifth and Eighth Circuits' conclusions that generic manufacturers could not unilaterally issue DHCP letters were erroneous. Opp. Br. 36 n.30. In fact, the FDA stated that a letter that warns about risks of a product constitutes labeling and must conform to the sameness provisions applicable to labeling. US Cert. Br. 17-18. Respondents also argue that DHCP letters are not subject to the same labeling requirement because they constitute promotional labeling. Opp. Br. 36-37. But FDA regulations define labeling broadly to include "[b]rochures, booklets, mailing pieces . . . letters . . . containing drug information supplied by the manufacturer." 21 C.F.R. § 202.1(*l*)(2); *see also* 21 U.S.C. § 321(m). This obviously includes promotional materials. As the United States notes, the DHCP letter that plaintiffs envision would have been subject to 21 C.F.R § 201.100(d), which requires it to be "consistent with and not contrary to [the drug's] approved . . . labeling." US Br. 18-19.

Further, FDA defines promotional labeling as materials "used to help sell prescription drugs." FDA, *Drug Advertising: A Glossary of Terms*, *available at*

www.fda.gov/Drugs/ResourcesForYou/Consumers/PrescriptionDrugAdvertising/ucm072025.htm (last visited Mar. 22, 2011). DHCP letters are intended to alert health care providers about important new information. Under no reasonable interpretation can DHCP letters be characterized as promotional labeling.

Even if the Court does not find the statutory and regulatory provisions clear on their face, as discussed above, FDA's interpretation of those requirements is entitled to deference.

C. Arguments That Plaintiffs Will Be Deprived of One Potential Defendant and/or That the Statutes Create an Anomaly Are Not Grounds for Finding That There Is No Preemption.

Plaintiffs accuse the generic drug manufacturers of seeking a special immunity that would deprive plaintiffs of any remedy, and creating arbitrary distinctions between classes of patients "based on the vagaries of pharmacy practice." Opp. Br. 2, 51-52. The real issue, however, is whether a generic drug manufacturer may be sued under state law for failing to do something that it is forbidden to do under federal law. Under the Supremacy Clause, the States may not enact laws that are inconsistent with the laws of Congress, and since this Court's decision in *Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 521-23 (1992), this principle applies to jury verdicts. Thus, even if a ruling on preemption in this case deprived injured patients who take generic

drugs of any remedy, or Hatch-Waxman's "same as" language creates an anomalous distinction between patients prescribed brand or generic drugs, that outcome would not be a basis for finding no preemption where there is a conflict between federal and state law.

Moreover, plaintiffs are incorrect that a holding of preemption in this case would deprive injured patients of any remedy. While "off-label prescribing" is not a violation of federal law, that fact does not absolve physicians from state law claims for prescribing metoclopramide for unapproved long-term use. *See, e.g., Sherrill v. Souder*, 325 S.W.3d 584 (Tenn. 2010) (malpractice claim for long-term prescription of Reglan). The metoclopramide label has explicitly warned that the risk of developing tardive dyskinesia "increase[s] with the duration of treatment," and that treatment for more than 12 weeks "has not been evaluated and cannot be recommended" since 1985. *See* Actavis Br. 8-9. In 2004, while both plaintiffs were using the drug, FDA approved a label change indicating: "Therapy should not exceed 12 weeks in duration." *Id.* at 10. In the face of such a specific warning, Dr. Graves, an *amicus* who treated Mrs. Demahy, prescribed the drug for 4 years. *See Amicus Curiae* Brief of Dr. Christy Graves at 1.[1]

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[1] The linchpin of Dr. Graves' argument is that during all relevant periods "the warnings in the labeling for metoclopramide asserted that it carried a low risk – only 0.2% or 1 in 500 – of [EPS which includes] tardive dyskinesia" although "[t]he actual risk . . . was in fact at least 100 times higher." Graves Br. 3. Dr. Graves is apparently unaware that

II. These Consolidated Cases Are Not an Appropriate Vehicle for Deciding, in the Abstract, Whether a Possible State Law Claim That Generic Manufacturers Must Ask FDA To Support a Label Change Is Preempted.

Respondents and the United States seek a ruling on whether a claim of liability for failure to ask FDA to support a change in the brand and generic label is preempted. Because this claim was not adequately pleaded below, the complaints should be dismissed. In any event, this case is not an appropriate vehicle for a ruling on any potential preemption issue related to this new claim, because it was never defined below, because respondents have cited no authority finding a failure to warn where the defendant has no direct control over its warning, and because it is unclear whether plaintiffs could ever prevail on such a speculative claim.

A. Plaintiffs' Current "Failure-to-Ask" Theory Was Not Pleaded by Plaintiffs, Nor Was That Claim Defined by the Courts Below.

The theory of liability now advanced by plaintiffs has morphed considerably from a classic failure-to-warn claim. While plaintiffs now assert that generic drug manufacturers are liable for failing

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the initial statement on the 2009 label that the prevalence of tardive dyskinesia is 20% was withdrawn as an error, and that today the 0.2% figure which she disputes remains on the label. *See* pp. 15-17, *infra*.

to ask FDA to support a label change, in their complaints, the plaintiffs asserted simply that generic drug defendants' failure to warn physicians of new information about the risks of metoclopramide caused plaintiffs' injuries. Since plaintiffs' direct failure-to-warn claims are preempted and since they did not plead their new failure-to-ask claims in their complaints, this Court should direct that all plaintiffs' claims be dismissed.

In the courts below, neither plaintiffs nor the courts discussed how plaintiffs' new claims would fit into applicable state law, including, for example, whether such claims could be brought as product liability failure-to-warn claims, as general negligence claims or under some other legal theory. And when the purported state law duty is analyzed in the context of metoclopramide's regulatory record, it becomes clear that the abstract preemption positions advocated by plaintiffs are seriously flawed. This Court therefore should limit its decision to the claims and record presented, which require dismissal.[2]

Plaintiffs' complaints in the district courts articulated classic direct failure-to-warn claims. The complaints are grounded on the assumption that a generic drug manufacturer had control over its labeling and could unilaterally make a change. The complaints do not assert that the generic drug

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[2] If the Court reaches the issue of whether this new "take steps" claim is preempted, Actavis agrees with PLIVA that the claim is preempted because it is dependent upon speculation regarding Agency actions and unduly interferes with FDA's chosen means and methods for carrying out the "same as" mandate of Hatch-Waxman.

manufacturers should have asked FDA to support a label change or, more precisely, urged the brand manufacturer to change its label. For example, Mensing alleged in her First Amended Complaint that "[t]his case involves DEFENDANTS' failure to warn doctors and patients of information within its knowledge or possession," JA 182 (¶ 41); "DEFENDANTS failed to use reasonable care to modify the package insert," JA 195 (¶ 93); "[Defendants] failed to promptly respond to and adequately warn about these risks," JA 199 (¶ 114); *see also* JA 193 (¶ 85), JA 204-05 (¶ 133).[3] Demahy's complaint similarly presumed the generic manufacturers' control over the label: "Defendants had a duty and obligation to disclose to plaintiff and her physicians the true facts concerning Reglan and/or metoclopramide." JA 441 (¶ 33).[4]

In their briefs to the district court, plaintiffs for the first time floated an argument that the generic drug manufacturers should have suggested a label change to FDA. That argument was made in response to the defendants' preemption arguments,

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[3] Indeed, in the sections of her complaint that identify the specific causes of action, Mensing made the allegations against all defendants, which included both the brand manufacturer and several generic manufacturers, with no acknowledgement of the fact that they were differently situated with regard to their ability to effect a label change. JA 198-219.

[4] Demahy's complaint does assert that Actavis "failed to fully, truthfully and accurately disclose Reglan and/or metoclopramide data to the FDA." JA 437-38 (¶ 20). The complaint does not identify what "data" was not disclosed and how these failures create a cause of action under Louisiana products liability law.

and was not described as a separate theory of state law liability. Moreover, plaintiffs did not identify the source of that duty. The scope of this newly-asserted duty also has been uncertain throughout the litigation. While plaintiffs assert in this Court that their remaining theories are still the standard, *Wyeth*-like failure-to-warn claims that were asserted in their complaints (Opp. Br. 21, 44), the claims now being advanced are in fact profoundly different, as both lower courts implicitly recognized.[5]

In a typical failure-to-warn case, the issues – as plaintiffs note – are (a) whether the warning was inadequate and, if so, (b) whether the absence of an adequate warning caused plaintiff's injury. Opp. Br. 41-44. The underlying assumption in these typical cases, however, is that the defendant had control over its label and could have added a warning upon learning of the new information that warranted the change. Here the generic drug manufacturers did

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[5] The United States also attempts to assist respondents in defining the take steps claim by stating that, even though no formal process was available for generic drug companies to revise their labels, a generic drug company could direct their proposals to the Office of Generic Drugs. US Br. 20-21. In fact, FDA has no process in place that specially addresses the evaluation of a request by the generic manufacturer to add a warning to its label. The internal guidance that the United States cites (*MAPP* 5200.6) outlines procedures for issuing and tracking consults in the Office of Generic Drugs. The fact that one of the 40 listed reasons for requesting a consult that appears on the form is "labeling revision" is not instructive. There is nothing to indicate that the revisions referred to have anything to do with warnings or that they should be initiated by the ANDA applicant as opposed to being done to conform to the brand reference listed drug.

not have such control; the brand manufacturer did. At most, the generic manufacturer could petition FDA to ask the brand manufacturer to make the label change, which, even if ultimately agreed to, might not have been made for a substantial period of time. Plaintiffs have cited no authority finding a failure-to-warn claim where the defendant does not have any direct control over its warning. None of the district or appellate courts below explained how the claim that plaintiffs now assert is actually viable under the law of either state.

B. Liability Under Plaintiffs' Current Theory Would Be Purely Speculative.

1. Any Hypothetical Duty to Seek a Label Change Is Inconsistent With the Regulatory Record for Metoclopramide.

The United States suggests that a hypothetical state law "failure-to-ask" claim could be based on a federal duty imposed on manufacturers of generic drugs to suggest or propose warnings to FDA (US Br. 26), while acknowledging that "[s]ituations where an ANDA holder alone has a basis to believe stronger warnings should be added to its drug's approved labeling have not been known to arise frequently" (*Id.* 20-21). In fact, we are not aware of a single instance where this has ever occurred and none has been identified by the government. The regulatory record here dramatically confirms that generics had

no information unknown to FDA on the key risk issue.

Here, plaintiffs assert that the risk of tardive dyskinesia is much higher than the label indicates. But the fact that the risk of tardive dyskinesia increases when the drug is used beyond its indicated usage of 12 weeks was well known to FDA and is contained throughout the record in the 2005 *Pozen* hearings that were before the *Mensing* court.[6] Indeed, based on its own 2002 to 2004 study of metoclopramide usage, FDA was aware of the exact percentages of use beyond 12 weeks and of the increased risk caused by that fact.[7] Nevertheless, FDA did not order a label change until long after the plaintiffs in these two cases stopped using the drug.

Plaintiffs state that in connection with the 2009 label change FDA "ordered the manufacturers to add information in the warning section of the label

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[6] *See* Actavis Br. 11-12.

[7] *See* Memorandum from Sigal Kaplan, June 10, 2005, Dkt. Entry 78, *Mensing v. Wyeth, Inc.*, 07-cv-3919 (Exh. HH to Second Clark Affidavit at 2-4). This data was submitted for publication in 2006: Sigal Kaplan, Judy A. Staffa & Gerald J. Dal Pan, *Duration of Therapy With Metoclopramide: A Prescription Claims Data Study*, 16 PHARMACOEPIDEMIOLOGY & DRUG SAFETY 878, 879 (2007). Plaintiffs cite to the studies mentioned in *McNeil v. Wyeth*, 462 F.3d 364 (5th Cir. 2006) as demonstrating the inadequacy of the warning. Opp. 9. All of these articles were specifically referred to in a May 18, 2004 memorandum by Dr. Eric Bastings during the *Pozen* review. *See* Memorandum of Eric Bastings, May 18, 2004, Dkt. Entry 78, *Mensing v. Wyeth, Inc.*, 07-cv-3919 (Exh. FF to Second Clark Affidavit at 7-12); *see also* Memorandum from Mary Ross Southworth, May 5, 2005. Dkt. Entry 78, *Mensing v. Wyeth, Inc.*, 07-cv-3919 (Exh. GG to Second Clark Affidavit at 4-5).

that a published study had found tardive dyskinesia occurring in 20 percent of the patients treated for at least three months . . . a hundred times greater than the 0.2 percent risk previously identified on the label." Opp. Br. 11. This is highly misleading because it mixes apples and oranges in two different ways. First, the 0.2% risk number is not for tardive dyskinesia but for extrapyramidal symptoms (EPS), a larger grouping of movement disorders, which includes tardive dyskinesia. Second, the 20% figure is a prevalence estimate and the 0.2% in an incidence figure.[8] But even more importantly, FDA has retracted the 20% prevalence reference, stating that "[i]nadvertent editing has resulted in inaccuracies regarding the representation of the data reviewed." Letter from FDA to Alaven Pharmaceuticals, LLC, July 20, 2010 (Addendum at 1a). As a result, the metoclopramide label no longer contains the 20% prevalence statement.

With this statement removed, the only changes remaining from the 2009 order are the black box itself and a new statement linking use beyond 12

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[8] Incidence measures how many people develop a disease in a given time frame (*i.e.* the number of new cases that develop in a year) and prevalence measures what percentage of the population has a disease. The most recent medical literature on these measures in relation to tardive dyskinesia comes from the Mayo Clinic and concludes that the risk (incidence) of tardive dyskinesia from metoclopramide is likely to be less than 1%. A.S. Rao & M. Camilleri, *Review Article: Metoclopramide and Tardive Dyskinesia*, 31 ALIMENTARY PHARMACOLOGY & THERAPEUTICS 11, 14-16 (2010). That low level is confirmed by the Shaffer study cited by plaintiffs, which reported 87 adverse reaction reports from 1992 to 2003 but which reported 50,000,000 prescriptions during that time. *See* Opp. 9.

weeks to the risk of tardive dyskinesia, although the label had previously stated that "[b]oth the risk of developing [tardive dyskinesia] and the likelihood that it will become irreversible are believed to increase with the duration of treatment and total cumulative dose." *See* Actavis Br. at 8-11. The statement about the risk of EPS, including tardive dyskinesia, being 0.2%, to which plaintiffs so strenuously object, has remained on the label throughout. Significantly, plaintiffs have never suggested that the 2009 label was insufficient; instead the claim is that the generic manufacturers should have requested FDA to make the 2009 changes earlier.

There is no basis for the plaintiffs' claim that the generic manufacturers had a duty to request FDA to amend the warning on metoclopramide to state that the risk of tardive dyskinesia was 20%. In fact, when FDA considered that issue in 2009, it made an explicit decision not to place such information on the metoclopramide label. If this is plaintiffs' claim, as they apparently contend in this Court, then the claim is preempted as having been explicitly rejected by FDA. *Wyeth*, 129 S. Ct. at 1198-99.

2. The Court Should Allow the State Courts to Decide Burden of Proof and Other Issues Regarding Any Failure-to-Ask Claim.

Both the Fifth and Eighth Circuits relied on this Court's statements in *Wyeth* about the burden that defendant Wyeth would bear in asserting a

preemption defense if it were to attempt to demonstrate that FDA would not have accepted the label change that plaintiffs advocated. JA 414, 555-56. Neither court recognized that whether the question of FDA action arises as part of the basic element of plaintiff's claim (as it could if the claim were that the generic manufacturer had a duty to ask FDA to support a label change) or a part of a preemption defense will affect which party has the burden of proof. Given the history of lower courts misinterpreting the meaning of *Wyeth* on the conflict preemption issue and on this issue, it is critical that the Court clarify that nothing in *Wyeth* affects the authority of state courts to define the elements of any claim that plaintiffs might be permitted to bring, including the allocation of the burden of proof.

Wyeth v. Levine was a classic failure-to-warn case, in which the drug manufacturer had the authority to make unilateral changes to its label and, this Court concluded, the record developed at trial indicated that the manufacturer had new information justifying such a revision. The one situation where the Court recognized that there could be preemption is where the defendant could show that FDA would have rejected a stronger warning label, but because preemption is a defense this Court concluded that there would be no preemption "absent clear evidence that the FDA would not have approved the change to [the] label" of the drug at issue there. 129 S. Ct. at 1198.

It is important, however, that this Court make it clear to the lower courts that its statements about the burden of proof in *Wyeth* have no applicability to

liability cases that may be brought against generic manufacturers that cannot make a label change. If the courts below allow plaintiffs to bring a claim for failing to ask FDA to support a label change, then those courts should be free to decide whether under state law plaintiffs should have the burden of demonstrating not only that the generic manufacturers had a duty to provide additional information to FDA, but that FDA and the brand manufacturers would have acted on that information. Unless this Court makes it clear that its statements about the burden of proving FDA action in the context of a preemption defense have no applicability here, there is a distinct risk that the lower courts will incorrectly apply the Court's statements regarding the burden of proof in *Wyeth* just as they almost uniformly and incorrectly have held that this Court's holding about the ability of a brand to unilaterally change its label applies in actions against generic manufacturers.[9]

C. The United States' New "Misbranding" Argument, Like Respondents' "Take Steps" Argument, Is Not Sufficiently Developed to Guide a Preemption Determination.

As previously noted, plaintiffs' cases should be dismissed because the only failure-to-warn claims alleged in their complaints are preempted. Plaintiffs

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[9] The Solicitor General agrees that the burden of proof issue is an issue of state law which should not be resolved by this Court. US Br. 32.

claim that the generic manufacturers have "imagined" that, in the absence of the ability to use the CBE regulation, liability is now being premised on a "take steps" claim, rather than a straightforward inadequate warning claim where the ability of the defendant to make a label change is not part of the plaintiffs' case-in-chief. Opp. 44. But the take steps claim that defendants refer to comes directly from both plaintiffs' briefs and the *Mensing* decision. In the Courts of Appeal, both Mensing and Demahy stated that "failure even to seek such approval [through the PAS process] was negligent and actionable." Appellant's Opening Br., *Mensing*, 2008 WL 5707474, at 30-31 (filed Feb. 20, 2008); Br. of Appellee, *Demahy*, 2009 WL 6297313, at 28-29 (filed Mar. 30, 2009); *see also* JA 402, 416. These latter claims sound in negligence for failure of a duty to seek a change from FDA, not for a failure to warn.

The uncertainties surrounding the nature and scope of plaintiffs' new claim, and how preemption principles might properly apply to them, are illustrated by the new argument that has been raised for the first time in the *amicus* brief filed by the United States. The government suggests that a federal duty on the part of generics to ask FDA to adopt stronger warnings arises from the need to reconcile the FFDCA's misbranding provision and the "same as" labeling requirement for generics in Hatch-Waxman. US Br. 25-29. There are several flaws in the United States' argument.

First, the government asserts that generic manufacturers are "obligated . . . to seek to revise their labeling" because commentary in the Federal

Register instructs generic manufacturers to "contact" FDA with "new safety information," but concedes that instances in which a generic manufacturer might possess such information would be so infrequent and factually "unique" that FDA has not promulgated any regulation to implement that "contact." US Br. 20-21.

Second, based on that tenuous foothold, the government "[f]ocus[es] the preemption inquiry on the standard in 21 C.F.R. § 201.57(e)" – the regulation that imposes a duty on drug manufacturers to revise their labeling "as soon as there is reasonable evidence of an association of a serious hazard with a drug." US Br. 27. Again, the government does not cite to any regulation which a generic manufacturer could use to revise its labeling even if it possessed such information. Nor does the government offer any example of a generic manufacturer's "compliance" with this federal "duty." That is because the theoretical process described is not the way the generic industry operates under Hatch-Waxman.

Hatch-Waxman was superimposed on an existing system in which FDA and the brand manufacturer constituted the sources of knowledge about a drug – the hubs that received, evaluated and acted upon information that they themselves created (*i.e.*, through clinical studies) or that they received from numerous spokes – physicians, pharmacists, consumers, etc. (*i.e.*, adverse event reports). None of the spokes had the authority to change drug labeling, and no state law holds such information sources liable for "inadequate" warnings. Hatch-Waxman

and its implementing regulations place generics in the same position, imposing a duty on generics to forward similar information to FDA, while maintaining the generic drug label the "same as" the brand drug label.

The system envisioned by Hatch-Waxman works, as amply demonstrated in the regulatory record described above. *See* Section II.B.1. All of the information that plaintiffs claim should have led to a labeling change prior to 2009 was considered by FDA at the *Pozen* hearings in 2005. The government does not argue to the contrary.

Instead, the government justifies the imposition of label revision responsibilities on generic manufacturers because otherwise generic drugs could have inadequate warnings but not be "misbranded." US Br. 29. That argument places the entire generic industry in an untenable position by essentially classifying generic drugs as "misbranded" in hindsight, based on a jury verdict that a label that the generic manufacturer had no power to change was "inadequate." Even if the manufacturer were to "propose" a change, its drug would *still* be misbranded until such time as FDA (which does not consult with a generic manufacturer regarding labeling changes) requires the brand manufacturer to make a change to its labeling. The government's qualification that "[a] misbranding determination in a private tort suit would not, of course, bind FDA in the exercise of its regulatory authority" (US Br. 32, n.16) provides cold comfort to a generic manufacturer exposed to state court liability based on jury

conclusions that its drug was "misbranded" due to inadequate labeling it had no power to change.

The government's new argument simply echoes the *Mensing* court's suggestion that generic drug manufacturers either be subject to state law claims that their drug labeling is "inadequate," or "simply stop[] selling the product." JA 416. As the United States recognizes elsewhere in its brief, the more logical way to interpret regulations promulgated for brand manufacturers is to give force to Hatch-Waxman's mandate for uniform labeling (labeling the "same as" brand drugs). *See, e.g.*, US Br. at 15-16 & n.8 (noting that as applied to an ANDA holder, the CBE regulation must be interpreted to mean that generic manufacturers may unilaterally change their labeling to make it uniform with a brand drug's labeling – not to add or change warning language).

Further, while the United States argues that plaintiffs' new claims against generic drug manufacturers are not categorically preempted, it has acknowledged the merits of the argument for impossibility preemption in cases where the label is not misbranded and a state court finds liability against the generic manufacturer (US Br. 29) and that certain kinds of claims, such as an alleged failure of a generic drug manufacturer to develop its own clinical trials, could be preempted. US Cert. Br. 21-22; US Br. 28 n.14. And, as we point out above, if the heart of plaintiffs' claim is that the generic manufacturers should have requested a warning declaring that the prevalence of tardive dyskinesia is 20% (*see* Opp. 6-11), as plaintiffs argue in this Court,

then FDA has already explicitly rejected that warning. Hence even plaintiffs' take steps case would be preempted. *Wyeth*, 129 S. Ct. at 1198-99. This Court should thus decline to consider the United States' argument in the abstract.

The variety of potential approaches and results simply highlights that these consolidated cases – with all their uncertainties and hypothetical claims – do not present a viable vehicle for determining the boundaries of preemption. The preemption inquiry should be considered when a concrete case presents it.

CONCLUSION

The claims that plaintiffs pleaded and pursued – that Actavis allegedly breached a duty to provide plaintiffs' physicians with new information on risks associated with the long-term use of metoclopramide – are in direct conflict with the "same as" labeling requirement of Hatch-Waxman and are preempted. The decisions below should be reversed and remanded with directions to dismiss all claims.

Respectfully submitted,

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March 23, 2011

APPENDIX

APPENDIX

[LOGO]
Department Of Health And Human Services

Food and Drug Administration
Silver Spring MD 20993

PRIOR APPROVAL SUPPLEMENT REQUEST

NDA 17854
NDA 21793

Alaven Pharmaceuticals, LLC
Attention: Mary Alonso
Manager, Regulatory Affairs and Drug Safety
2260 Northwest Parkway, Suite D
Marietta, GA 30067

Dear Ms. Alonso:

Please refer to your new drug application (NDA) for Reglan (metoclopramide) Tablets and Reglan ODT (metoclopramide orally disintegrating tablets) 5 mg, 10 mg.

We have reassessed the statements regarding Tardive Dyskinesia in the Warnings and Precautions Section of the prescribing information. Inadvertent editing has resulted in inaccuracies regarding the representation of the data reviewed.

We request that the following changes in the labeling be made so as to furnish adequate information for the safe and effective use of the drug:

Tardive Dyskinesia (see Boxed Warnings)

Treatment with metoclopramide can cause tardive dyskinesia (TD), a potentially irreversible and disfiguring disorder characterized by involuntary movements of the face, tongue, or

extremities. The risk of developing tardive dyskinesia increases with the duration of treatment and the total cumulative dose. An analysis of utilization patterns showed that about 20% of patients who used metoclopramide took it for longer than 12 weeks. Treatment with metoclopramide for longer than the recommended 12 weeks should be avoided in all but rare cases where therapeutic benefit is thought to outweigh the risk of developing TD.

Although the risk of developing TD in the general population may be increased among the elderly, women, and diabetics, it is not possible to predict which patients will develop metoclopramide-induced TD. Both the risk of developing TD and the likelihood that TD will become irreversible increase with duration of treatment and total cumulative dose.

Metoclopramide should be discontinued in patients who develop signs or symptoms of TD. There is no known effective treatment for established cases of TD, although in some patients, TD may remit, partially or completely, within several weeks to months after metoclopramide is withdrawn.

Metoclopramide itself may suppress, or partially suppress, the signs of TD, thereby masking the underlying disease process. The effect of this symptomatic suppression upon the long-term course of TD is unknown. Therefore, metoclopramide should not be used for the symptomatic control of TD.

We request that you submit draft labeling as a prior approval supplement to this application. Incorporate all previous revisions as reflected in the most re-

cently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes that are being made.

The supplement should be submitted within 30 days.

If you have any questions, call Maureen Dewey, Regulatory Project Manager, at (301) 796-0845.

Sincerely,

[See appended electronic signature page]

Joyce Korvick, M.D., M.P.H.
Deputy Director for Safety
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/ Number	Submission Type/ Number	Submitter Name	Product Name
NDA-21793	GI-1	Alaven Pharmaceutical LLC	Reglan RPT (Metoclopramide) *5/10* MG TABS
NDA-17854	GI-1	Alaven Pharmaceutical LLC	Reglan

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/s/

JOYCE A KORVICK
07/20/2010

REPLY BRIEF

Supreme Court, U.S.
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Nos. 09-993 VIDE 09-1039, 09-1501

In The Supreme Court of the United States

PLIVA, INC., ET AL., 09-993 *vide* 09-1039, *Petitioners*,

v.

GLADYS MENSING, *Respondent*.

ACTAVIS ELIZABETH LLC, 09-1039 *vide* 09-993, *Petitioner*,

v.

GLADYS MENSING, *Respondent*.

ACTAVIS INC., 09-1501, *Petitioner*,

v.

JULIE DEMAHY, *Respondent*.

On Writs of Certiorari to the U.S. Courts of Appeals for the Fifth and Eighth Circuits

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INTRODUCTION

Respondents virtually abandon the primary position they took below, and which most lower courts have adopted—that generic companies are subject to state-law failure-to-warn liability no less than branded companies, because they have no less power than branded companies to alter their warnings unilaterally. As the government explains, that position is manifestly incorrect. In contrast to branded companies, federal law precludes generic companies from altering their warnings unilaterally. That fundamentally distinguishes *Wyeth*. Here, generic companies are prohibited from altering their warnings not only by "specific agency regulation[s] bearing the force of law," *cf. Wyeth v. Levine*, 129 S. Ct. 1187, 1203 (2009); *id.* at 1204 (Breyer, J., concurring), but by the Hatch-Waxman Act itself.

That should be the beginning and end of this case. Under conflict preemption principles as old as our republic, state law cannot punish petitioners for using the warnings federal law compelled them to use. *See Gibbons v. Ogden*, 22 U.S. 1, 210 (1824). And because courts across the country are allowing juries to render massive verdicts—including punitive damages—based on the false premise that generic defendants simply could have printed new labels, it is essential that this Court reverse *Demahy*'s holding that generic companies can act unilaterally.

Undeterred, respondents seek to avoid federal law's preemptive effect by asserting a novel alternative theory. They claim that even if federal law precluded petitioners from communicating different warnings *to them*, petitioners should have

communicated with *a federal agency* that has sole authority to approve generic warnings, and which in turn *might have* authorized a change. That theory, which hinges on a hypothetical state-law "duty to ask FDA," provides no refuge.

To begin with, the very existence of that duty is dubious. Though respondents assert their claims are "traditional," neither they, the lower courts, nor their *amici* identify any case recognizing this exotic *state-law* duty to communicate with a *federal agency*. Instead, they simply assume its validity, and then seek to mold the malleable contours of that novel duty to their needs.

This Court need not resolve respondents' state-law contentions, however, because federal law preempts their state-law theory in any event. The Supremacy Clause forecloses state-law claims that depend on speculation about how a federal agency would exercise its exclusive authority, *Arkansas La. Gas Co. v. Hall* ["*Arkla*"], 453 U.S. 571 (1981), or that otherwise impose or enforce duties to a federal agency, *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341 (2001). Those principles are dispositive.

As respondents eventually concede, FDA's hypothetical response to a proposed labeling change is "relevant" (*read*: dispositive) to whether federal law allows their claims to proceed. Resp. Br. 41 n.35. *Arkla* therefore is indistinguishable. It held that the plaintiffs' traditional breach-of-contract claims were preempted because federal law gave the Federal Power Commission sole authority to approve gas rates (just as federal law gives FDA sole authority to approve generic labeling), and because speculating about how FPC might have exercised that authority

usurped FPC's authority (just as speculating about FDA's response here would usurp *its* authority).

The government's alternate claim that respondents' *state* claims can proceed *only* because they are premised on violations of an alleged *federal* duty to ask FDA fares no better. That novel federal duty is as dubious as the novel state-law duty respondents concoct. Indeed, it rests on the same "inherently suspect" source *Wyeth* rejected: a preamble the government admits is not tied to a "formal regulation." *Compare* U.S. Br. 21 *with Wyeth*, 129 S. Ct. at 1201.

But even if that alleged *federal* duty does exist, it would not support *state-law* claims. As *Buckman* recognized (at the government's urging), Congress gave the *federal* government exclusive authority to enforce obligations to communicate *to FDA*, because communications between regulated parties and their *federal* regulators are inherently *federal*. The government's current position directly conflicts with its past representations, and the government hardly tries to reconcile it.

Make no mistake: Petitioners are not suggesting they have no obligation to ensure the safety of their products, or that they are immune from liability. *Federal law* requires generic companies to communicate adverse event data to FDA, and *the federal government* has plenary authority to enforce those obligations. But as the government recognized in *Buckman*:

> If federal regulatory agencies are to perform the important functions assigned to them by Congress, they must have the ability to decide, free from hindrances imposed by state law,

> how best to obtain the information they need and how to sanction those who fail to provide such information.

Br. of the U.S. as *Amicus Curiae*, *Buckman*, 2000 WL 1364441, *18 (Sept. 13, 2000) ["*Buckman* Br."]. The government's desertion of its *prevailing* position in *Buckman* is inexplicable—and this Court should not countenance its attempt to abdicate the enforcement authority Congress reserved to the United States.

ARGUMENT

I. FEDERAL LAW PREEMPTS STATE-LAW CLAIMS THAT PETITIONERS WERE OBLIGATED TO ALTER THEIR WARNINGS.

The government's brief confirms that petitioners "could not properly have invoked the CBE or PAS process, or sent [a Dear Doctor] letter." U.S. Br. 12. Instead, federal law precludes generic companies from unilaterally altering their warnings, by repeatedly requiring that branded and generic warnings be "the same." *See* PLIVA Br. 30-47; U.S. Br. 14-19. The ordinary operation of the Supremacy Clause thus bars state-law failure-to-warn claims: Generic companies cannot simultaneously fulfill a federal duty to provide "the same" warnings and a state-law duty to provide "different" ones. *See, e.g.*, *Hillsborough Cnty., Fla. v. Automated Med. Labs., Inc.*, 471 U.S. 707, 713 (1985); *see also Geier v. American Honda Motor Co.*, 529 U.S. 861, 873 (2000); *Florida Lime & Avocado Growers, Inc. v. Paul*, 373 U.S. 132, 142-43 (1963).

A. Petitioners Could Not Have Used The CBE Process.

Respondents no longer defend *Demahy*'s remarkable assertion that the sameness requirements apply only before approval, JA534-35. Instead, and despite FDA's longstanding position that generics may not use the CBE process to deviate from the branded warnings, *see* PLIVA Br. 19-20, 32-36, 41-43, respondents now insist that the sameness requirements do not actually preclude generics from using different warnings at all—and thus that petitioners unilaterally could have executed changes via CBE. Resp. Br. 33-35.

Their contention rests on an FDA regulation that allows generics unilaterally to implement certain "'labeling revisions made to comply with current FDA labeling guidelines or other guidance.'" *Id.* 34 (quoting 21 C.F.R. § 314.94(a)(8)(iv)). But there is a simple reason why even *Demahy* did not invoke this narrow exception: FDA did not issue "labeling guidelines or other guidance" that would have allowed petitioners to alter their metoclopramide warnings, so there was never a pertinent FDA guidance with which such changes would have "compl[ied]." *See also* U.S. Br. 16 n.7. And construing this narrow exception to permit changes absent a prior FDA directive would swallow the sameness rule, by allowing disparate warnings any time a generic company wants. Respondents' distortion of this narrow exception is meritless.

B. Petitioners Could Not Have Used The PAS Process.

Respondents no longer claim that the PAS regulation's authorization for changes that "are not

limited to" those specifically enumerated somehow overrides the regulation's specific "except[ion]" of changes "described in [the CBE subsection]." *Compare* 21 C.F.R. § 314.70(b)(2) *with id.* § 314.70(b)(2)(v)(A). Instead, they now assert that the "except clause" simply grants the option of altering warnings through either a PAS or CBE. Resp. Br. 32.

That contrived interpretation does not help respondents, however, because "FDA does not interpret its regulation that way." U.S. Br. 17. Instead, FDA construes the "except" clause consistent with its plain meaning—as excepting from the PAS process any changes subject to the CBE process. *See id.* Respondents do not even try to argue that FDA's interpretation is "plainly erroneous or inconsistent with the regulation," and FDA's view thus is "controlling." *Auer v. Robbins*, 519 U.S. 452, 461 (1997) (quotation omitted).[1]

C. Petitioners Could Not Have Sent A "Dear Doctor" Letter With Different Warnings.

Finally, respondents assert that petitioners could have sent a Dear Doctor letter ("DDL") with different warnings, because such letters are "promotional labeling" allegedly "not subject to [the sameness]

---

[1] The sameness requirements would in any event "prevent approval of a PAS [that would] diverge from the RLD's approved labeling." U.S. Br. 17. While FDA nonetheless claims it "would not have ignored" an improper PAS, *id.* 18, FDA still would have had to approve the proposed change for the RLD before petitioners could have implemented and delivered it. *See* Br. 46 n.14; *see also infra* § 2.

requirement." Resp. Br. 36. That assertion is groundless. Generic and branded "labeling" must be "the same," *e.g.*, 21 U.S.C. § 355(j)(2)(A)(v), and "labeling" is all-encompassing: It includes "all labels and other written, printed, or graphic matter" regarding drugs. 21 U.S.C. § 321(m); 21 C.F.R. § 202.1(l)(2).

Respondents claim there is a "critical regulatory distinction" between labeling approved during FDA's initial review and post-approval promotional labeling. Resp. Br. 36. But that merely retreads *Demahy*'s false dichotomy between pre- and post-approval warnings, with equally unavailing results. DDLs are not "freestanding," but instead must be read "in tandem" with the approved labeling to which they relate—and so by law must be fully "'consistent with'" it. U.S. Br. 18-19 (quoting 21 C.F.R. § 201.100(d)(1)). That makes sense. The *sameness* requirements would be irrelevant if generics could evade them simply by dispatching *different* product warnings through other channels.

Because that is precisely how respondents assert petitioners should have used DDLs, their argument cannot be squared with FDA's regulations or Hatch-Waxman's premise: that generic and branded warnings must be "the same," because generic and branded products are therapeutically "the same." Federal law thus precludes claims that petitioners should have dispatched a DDL whose content deviated from petitioners' FDA-mandated warnings.

At bottom, generic companies are powerless to change their warnings unilaterally, and federal law thus preempts respondents' failure-to-warn claims.[2]

II. FEDERAL LAW PREEMPTS STATE-LAW CLAIMS THAT PETITIONERS WERE OBLIGATED TO ASK FDA FOR A LABELING CHANGE.

Effectively conceding that petitioners could not have changed their warnings unilaterally, respondents spend most of their brief arguing that *state law* can sanction petitioners' failure *to ask FDA* for a labeling change. That theory of liability has no basis in traditional state tort law, and is in any event foreclosed by *Arkla* and *Buckman*.

A. Respondents' Theory Is Unprecedented.

Respondents first assert that petitioners are "plucking a phrase out of context from [*Mensing*]" and "mischaracterizing Plaintiffs' claims." Resp. Br. 40. According to them, their claims are "traditional inadequate-warning claims, not the hypothetical 'take steps' claims imagined by Defendants." *Id.* 44. While respondents' *complaints* may have asserted "traditional" failure-to-warn claims, the novel theory of liability respondents advanced *in the appellate*

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[2] Finally, respondents assert that petitioners could have filed a "citizen's petition" asking FDA to modify the warnings. Resp. Br. 35-36 (citing 21 C.F.R § 10.30). Neither respondent raised this claim below, so neither appellate court addressed it. Waiver aside, FDA still would have had to approve such a petition before petitioners could have acted—just as FDA would have had to approve a PAS. *Supra* n.1.

courts—which gave rise to the decisions under review—is far from "traditional."

Indeed, petitioners are not alone in "imagining" that respondents now assert a novel state-law duty *to ask FDA*: The appellate courts likewise "imagined" that respondents were invoking "a duty under state law ... to propose stronger warnings" to FDA, JA413, because that is *precisely* how respondents described their claims. In Ms. Demahy's words, Actavis "could have sought to strengthen its warnings ... through the [PAS] process [and its] *failure even to seek such approval was both negligent and actionable*." Br. of Appellee, *Demahy*, 2009 WL 6297313, *28-*29 ["*Demahy* Br."] (Mar. 30, 2009) (emphasis added). Ms. Mensing used the very same words. Appellant's Opening Br., *Mensing*, 2008 WL 5707474, *30-*31 ["*Mensing* Br."] (Feb. 20, 2008).

Respondents are free to abandon that theory if they wish. In that case, the decisions should be reversed and judgment entered for petitioners: Again, federal law preempts traditional failure-to-warn claims because it is impossible for petitioners to comply with both a federal duty to issue *the same* warnings FDA approved for the branded product and a state-law duty to issue *different* warnings.

To the extent respondents continue pursuing their novel theory of liability, however, it is unprecedented. As petitioners noted in their opening briefs, neither appellate court cited any authority recognizing this novel theory. They simply assumed the existence of a "duty under state law ... to propose stronger warnings" to FDA, and then rejected preemption. JA413-14; *see also* JA555-56; JA558-59.

Respondents do no better here. They cite only two state-law cases, Resp. Br. 29-30, and neither involved a defendant who lacked the legal authority to warn consumers directly, yet nonetheless was held liable for failing to ask another party (much less *a federal agency*) for permission to use different warnings. *McCormack v. Hankscraft Co.*, 154 N.W.2d 488, 495 (Minn. 1967) (manufacturer of steam vaporizer could have warned consumer injured by "scalding hot" device); *Stahl v. Novartis Pharms. Corp.*, 283 F.3d 254 (5th Cir. 2002) (brand manufacturer could have warned consumers and physicians of drug risks, and did so). The cases respondents' *amici* cite likewise are inapposite. Br. of Torts Profs. 36-37 (cases holding that tobacco and all-terrain vehicle manufacturers could have warned users); Br. of Admin. Law & Civ. Pro. Profs. 23-24 (cases holding that commercial silica and heart valve manufacturers could have warned users).

Respondents' failure to identify such a case is not surprising. In our federal republic, there is no tradition of *States* regulating communications to *federal agencies*. *Buckman*, 531 U.S. at 353.

B. *Wyeth* Does Not Support Respondents' Theory.

Respondents nonetheless strain to fit their novel failure-to-ask-FDA claims into *Wyeth*'s framework, but it provides no support. *Wyeth* addressed traditional failure-to-warn-the-user claims, and this Court allowed the claims to proceed only because the CBE process allowed Wyeth to alter its warnings unilaterally: There is "an FDA regulation that permits a [branded] manufacturer to make certain changes to its label *before receiving the agency's*

approval." 129 S. Ct. at 1196 (emphasis added); *see also id.* at 1198 ("[T]he CBE regulation permitted [Wyeth] to provide such a warning *before receiving the FDA's approval*.") (same); *id.* at 1199 ("The CBE regulation permitted Wyeth to *unilaterally* strengthen its warning.") (same).

Respondents try to escape the obvious import of those statements by asserting that *Wyeth*'s CBE holding was immaterial. Resp. Br. 46. That claim is astonishing. The parties vigorously contested the CBE issue, *e.g.*, Br. for Pet'r, *Wyeth*, 2008 WL 2273067, *34-*40 (May 27, 2008); Br. of Resp., *Wyeth*, 2008 WL 3285388, *37-*43 (Aug. 7, 2008) ["Levine Br."], and the Court's resolution of that dispute was critical. Indeed, as the government acknowledges here, Wyeth's ability to use the CBE process is precisely what averted a conflict between its state-law duty and federal law. U.S. Br. 25 n.13 ("Wyeth had a duty to provide a warning ... and FDA's procedures gave Wyeth the means to do so. Wyeth, therefore, did not find itself in an impossible situation calling for preemption.") (quotations omitted). That is why the Court repeatedly stressed that Wyeth could have executed a CBE. 129 S. Ct. at 1196, 1198, 1199.

Respondents nonetheless claim that *Wyeth* turned on the proposition that "the manufacturer bears responsibility for ... its label," rather than on "the availability of a single procedure, CBE." Resp. Br. 45-46. But those are two sides of the same coin:

> [T]he CBE regulation ... both reflects the manufacturer's ultimate responsibility for its label and provides a mechanism for adding safety information to the label prior to FDA

> approval.... Wyeth had a duty to provide a warning that adequately described that risk, and the CBE regulation permitted it to [do so] before receiving the FDA's approval.

129 S. Ct. at 1198.

That reasoning compels a finding of preemption here. As set forth above, the CBE process does *not* allow generics to deliver new warnings without prior FDA approval. Instead, federal law *precludes* generics from exercising the powers it gives branded companies. Together with the sameness mandate (which *requires* generics to use the branded company's FDA-approved warnings), the fact that federal law withholds CBE authority from generic companies indicates that they do *not* have "ultimate responsibility" for the warnings they are obligated to use. *Cf. Wyeth*, 129 S. Ct. at 1198; *see also Abbreviated New Drug Application Regulations—Final Rule*, 57 Fed. Reg. 17950, 17961 (Apr. 28, 1992) ("[T]he [generic] labeling must be the same as the [branded] labeling because the [branded] product is the basis for [generic] approval."); *id.* ("FDA will determine whether the labeling for the generic and [branded] drugs should be revised.").

Indeed, FDA's approach when a branded company withdraws its product from the market powerfully illustrates this point. Though the Agency designates one of the remaining generic companies to serve as the new reference listed drug, it has made clear that FDA—not the designated generic company—bears responsibility for updating the product warnings:

> ANDAs that refer to [the withdrawn product] may be approved by [FDA] if all other legal and regulatory requirements for the approval

> of ANDAs are met. *If FDA determines that labeling for this drug product should be revised to meet current standards, the Agency will advise ANDA applicants to submit such labeling.*

Determination That Brethine (Terbutaline Sulfate) Injection Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness, 72 Fed. Reg. 39629, 39630 (July 19, 2007) (emphasis added). That policy underscores the fact that generics simply do not bear the same obligations as branded companies.

Despite this, respondents claim *Wyeth* requires petitioners to prove that FDA would have rejected a proposed change. Resp. Br. 45. But as the government again acknowledges, *Wyeth*'s brief discussion of this point flowed directly from its holding that branded companies can act unilaterally. That meant Wyeth could establish a conflict between state and federal law *only* by proving that FDA would have *rescinded* a change:

> "Wyeth had a duty to provide a warning...," and FDA's procedures gave Wyeth the means to do so. Wyeth, therefore, did not find itself in an impossible situation calling for preemption. In those circumstances, the Court understandably insisted upon "clear evidence" before it could "credit Wyeth's contention that the FDA would have prevented it from adding a stronger warning."

U.S. Br. 25 n.13 (quoting *Wyeth*, 129 S. Ct. at 1198-99).

By contrast, petitioners here have borne their burden of proving the "impossible situation" Wyeth

could not: Hatch-Waxman itself is "clear evidence" that petitioners cannot alter their warnings. It thus is plaintiffs—not defendants—who must speculate that FDA would have *approved* a proposed change.[3]

C. *Arkla* Forecloses Respondents' Theory.

Whatever the contours of this novel state-law theory, *Arkla* bars respondents' claims. In direct contrast to *Wyeth*—where the plaintiff's claims could have proceeded without referencing FDA—respondents' novel theory of liability necessarily runs *through FDA*, because it depends on claims that petitioners *should have asked FDA* to approve a labeling change. *Demahy* Br., 2009 WL 6297313, *28-*29; *Mensing* Br., 2008 WL 5707474, *30-*31.

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[3] Recognizing this straightforward point, respondents assert they need not speculate about FDA's response, because their claims only require proof that the existing warnings' inadequacy caused their injuries. Resp. Br. 42-44. But the secondary authorities respondents cite describe garden-variety failure-to-warn claims, where a defendant can warn consumers directly. Here, FDA's decisionmaking severs any link between the challenged conduct—what respondents below called petitioners' "failure even to seek ... approval" from FDA, *e.g.*, *Demahy* Br., 2009 WL 6297313, *28-*29—and respondents' injury. Without FDA approval, petitioners' failure to request a change could not have impacted respondents, and there would be no basis for imposing liability under basic state-law principles. *See, e.g.*, *Meany v. Meany*, 639 So.2d 229, 233 (La. 1994) (requiring "a causal relationship between the defendant's alleged negligent act and the plaintiff's injuries"); *Hudson v. Snyder Body, Inc.*, 326 N.W.2d 149, 157 (Minn. 1982) (requiring proof that defendant's "breach of duty was the proximate cause of plaintiff's injury"). That is why the Eighth Circuit recognized that respondents' theory ultimately rested on "speculation" about "what the FDA might have done." JA414.

That explains why respondents eventually concede that FDA's hypothetical response limits their ability to recover, even if they say that is so as a matter of federal rather than state law. *See* Resp. Br. 41 n.35.

That puts these cases on all fours with *Arkla*—where federal law likewise circumscribed the plaintiffs' recovery, because only FPC had authority to approve gas rates (just as FDA alone has authority to approve generic labeling changes). As *Arkla* explained, the lower court's judgment impermissibly rested on

> an assumption that the higher rate respondents might have filed with [FPC] was reasonable. Otherwise, there would have been no basis for that court's conclusion that [FPC] would have approved the rate. But under the filed rate doctrine, [FPC] alone is empowered to make that judgment, and until it has done so, no rate other than the one on file may be charged.

Arkla, 453 U.S. at 580-81 (citation omitted).

Respondents try to limit *Arkla* to the filed-rate context, asserting that the Natural Gas Act gave FPC the exclusive right to approve gas rates, while "'Congress did not intend FDA oversight to be the exclusive means of ensuring drug safety and effectiveness.'" Resp. Br. 55 (quoting *Wyeth*, 129 S. Ct. at 1200). But Congress (and FDA) plainly *did* intend that generic and branded product warnings be "the same," which is why respondents retreat to claims that "Defendants could have *sought FDA approval* for stronger warnings." Resp. Br. 22 (emphasis added). Put simply, at the point where respondents' claims come to depend on FDA's pre-

approval—a decision that *by definition* is vested in FDA, *see* U.S. Br. 7—*Arkla* is indistinguishable.[4]

The government's attempt to distinguish *Arkla* fares no better. Indeed, it directly contradicts the government's position in *Buckman* and *Warner-Lambert*, where it relied on *Arkla* to advocate preemption of the state-law claims in those cases—which, as here, sought to enforce alleged state-law duties to communicate with FDA. *See, e.g.*, *Buckman* Br., 2000 WL 1364441, *25-*26 (relying on *Arkla*); Br. for the U.S. as *Amicus Curiae*, *Warner-Lambert Co. v. Kent*, 552 U.S. 440 (2008), 2007 WL 4218889, *20-*21 (Nov. 28, 2007) (same) ["*Warner-Lambert* Br."]. The government *now* asserts that *Arkla* and its progeny are inapposite because they involved "the extraordinarily comprehensive authority the agencies in question had in their respective fields." U.S. Br. 30-31. And it expressly disavows its prior

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[4] Respondents also claim they need not speculate about FDA's hypothetical response because FDA ultimately ordered a labeling change and because evidence allegedly would have supported that change earlier. Resp. Br. at 38-39. But as Actavis well explains, FDA had the information respondents cite *years* before ordering a change—and even then, FDA rejected the principal change respondents are demanding. Actavis Reply Br. 14-17. In any event, respondents' characterization of the non-record evidence (and especially the self-serving claims of Ms Demahy's physician and *amicus curiae* Dr. Graves) is hotly contested. If the Court allows respondents' claims to proceed, those issues will be vigorously litigated—and the Court should not prejudice potential future proceedings by lending credence to the inaccurate factual claims set forth in those briefs.

submissions to this Court, claiming they were offered "without the benefit of ... *Wyeth*." U.S. Br. 31.

Those putative justifications for the government's about-face are meritless. *Arkla* did not depend on FPC's broad authority to regulate interstate gas distribution; it turned on the fact that the specific matter about which the Louisiana courts speculated—whether "the Commission would have approved the rate," *Arkla*, 453 U.S. at 581—fell within FPC's exclusive jurisdiction. *See id.* at 581-82 ("[T]he Commission alone is empowered to make *that judgment*.... The court below [thus] usurped a function that Congress has assigned to a federal regulatory body.") (emphasis added). That is equally true here: Only FDA can approve a generic warning change, and without its prior approval, petitioners could not have delivered any other warning.

Nor does *Wyeth* undermine the government's prior reliance on *Arkla*. To the contrary, *Wyeth*'s CBE holding meant the Court did not need to address *Arkla*'s dispositive implications for the claims respondents allege. Indeed, the plaintiff's fall-back argument in *Wyeth* foreshadowed the very claims here: She argued that Wyeth at least *could have sought* changes "by submitting a supplemental application for FDA approval," and further asserted that state law did not "require ... changes *without* seeking FDA's approval." Levine Br., 2008 WL 3285388, *37 (emphasis original). Wyeth in turn replied that *Arkla* foreclosed Levine's alternate theory of liability, because it would assign "juries the speculative task of determining whether and when FDA would have approved a particular hypothetical labeling change." Reply Br. for Pet'r, *Wyeth*, 2008

WL 4264481, *12 & n.7 (Sept. 15, 2008) (citing *Arkla*).

Wyeth declined to address those arguments, of course, because its CBE holding made doing so unnecessary. *Wyeth* thus provides no support for the government's decision to abandon its settled understanding of *Arkla*, and casts no doubt on *Arkla*'s dispositive application to respondents' novel theory of liability.

D. *Buckman* Forecloses The Government's Alternative Claims.

Though the government agrees with petitioners that federal law precludes generics from altering their warnings unilaterally, it apparently dislikes the preemptive result that follows. It thus seeks to evade that outcome by cobbling together a novel federal duty that just happens to mirror respondents' novel state-law claims. That effort is deeply flawed, but even on its own terms, the government's theory runs headlong into *Buckman*.

1. Federal Law Did Not Obligate Petitioners To Propose Labeling Changes To FDA.

The government begins by asserting—for the first time ever—that "ANDA holders ... have a duty *under federal law* to propose appropriate changes to approved labeling." U.S. Br. 14 (emphasis added). That the government *alone* makes this argument is the first sign of trouble: When even the plaintiffs fail to assert that their state-law claims mirror a preexisting federal duty, it is a sure indication that the alleged federal duty is made from whole cloth.

The government nonetheless purports to locate this duty in 21 C.F.R. § 201.57. But § 201.57 does not say that companies (whether branded or generic) have a duty "*to propose* appropriate changes," U.S. Br. 14 (emphasis added), or "*seek to* revise their labeling." *Id.* 20 (same). Instead, it says that product warnings *actually* "shall be revised" when new information warrants. 21 C.F.R. § 201.57.

As petitioners previously explained (and the government effectively concedes), generic companies could not fulfill the *actual* § 201.57 duty if it applied to them. *See* PLIVA Br. 37-41. After all, the sameness requirements prohibit generics from revising their warnings unilaterally. That strongly indicates that § 201.57 does *not* independently apply to generics: Federal law typically does not demand the impossible. Moreover, that language was promulgated in 1979, five years *before* Hatch-Waxman's enactment. *See Content and Format Labeling for Human Prescription Drugs—Final Rule*, 44 Fed. Reg. 37434, 37463 (June 26, 1979). That likewise indicates that the § 201.57 duty applies to branded companies who (unlike generics) *can* revise their warnings unilaterally through the CBE process (promulgated in 1965).

These points readily explain why—until now—FDA repeatedly made clear that generic companies are *not* independently subject to § 201.57, and why—until now—FDA never construed § 201.57 to impose the novel federal duty the government first identifies in its merits-stage brief. Instead, FDA consistently explained that generic companies comply with § 201.57 by ensuring that their labeling is "the same as" the branded labeling. PLIVA Br. 38-40 (quoting

Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics—Proposed Rule, 65 Fed. Reg. 81082, 81098 (Dec. 22, 2000); *Requirements on Content and Format of Labeling for Human Prescription Drugs and Biological Products—Final Rule*, 71 Fed. Reg. 3922, 3928 (Jan. 24, 2006)).

The government makes no effort to reconcile its litigating position with the views FDA repeatedly expressed during formal rulemaking proceedings. Instead, it relies on a comment in the preamble to a different final rule, U.S. Br. 20 (quoting 57 Fed. Reg. at 17961), and then concedes that "FDA has not promulgated a formal regulation for th[e] process" it claims was "contemplated" there. *Id.* 20-21. If that curious approach to administrative law sounds familiar, it is: In *Wyeth*, the government likewise relied on a preamble issued without notice or opportunity for comment, and this Court rejected it as "inherently suspect." *Wyeth*, 129 S. Ct. at 1201; *cf. id.* at 1204 (Breyer, J., concurring) (noting FDA's failure to rely on "lawful specific regulations").

In any event, the government's preambular theory fails on its own terms. The preamble did not even cite 21 C.F.R. § 201.57—much less "explain[] how ANDA holders should discharge their duty to provide adequate warnings" apart from mirroring the approved branded labeling. U.S. Br. 20. And rather than impose a legal *duty* on generic companies to request labeling revisions, it stated only that "*if* an ANDA holder *believes* that new safety information should be added, it *should* provide adequate supporting information to FDA, and *FDA*

will determine whether the labeling ... should be revised." 57 Fed. Reg. at 17961 (emphasis added).

Unlike "shall" or "must," the word "should" does not impose legal duties. *See, e.g., United States v. Maria*, 186 F.3d 65, 70-72 (2d Cir. 1999); *Marshall v. Anaconda Co.*, 596 F.2d 370, 375-76 (9th Cir. 1979); *Baptist Healthcare Sys. v. Sebelius*, 646 F. Supp. 2d 28, 35 (D.D.C. 2009). Even if it did, the duty would arise only "*if* an ANDA holder *believes*" a change is warranted, not when litigants (or FDA) later assert it was. 57 Fed. Reg. at 17961. Finally, the preamble's conclusion that "*FDA will determine*" whether to accept proposed changes, *id.*, fatally undermines the government's claim that juries are free to speculate about how FDA would have exercised powers that the Agency expressly reserved *to itself*. *Arkla*, 453 U.S. at 581.

Equally unprecedented is the government's assertion that a generic product which complies with the sameness mandate nonetheless can be "misbranded" if its manufacturer fails "to seek" a labeling change from FDA. U.S. Br. 26. The government relies on § 201.57 and the preamble for this point, but neither supports this extravagant claim (as explained above). Nor does the government identify any case in Hatch-Waxman's 27-year history where it brought a misbranding claim based on this novel theory. *See Wyeth*, 129 S. Ct. at 1197 (questioning FDA's theory of misbranding because FDA never brought suit under that theory). And the theory in any event is absurd: Misbranding turns on the label's content, not on whether the company contacted FDA; the label is either misbranded or not, and it is hard to see how sending FDA a letter

changes that. At bottom, it defies logic to say a generic product can be misbranded when it bears the very label federal law requires. *Cf. SmithKline Beecham Consumer Healthcare, L.P. v. Watson Pharms., Inc.*, 211 F.3d 21, 27 (2d Cir. 2000) (generic label that complied with sameness requirement cannot plausibly give rise to copyright infringement liability).

If FDA wants to establish a new federal duty to propose labeling changes, it can start rulemaking tomorrow. But it has no business urging this Court to impose an unprecedented federal duty that just happens to mimic respondents' unprecedented state-law theory.

2. Only The United States Can Enforce A Duty To Communicate With FDA.

Even if federal law did obligate petitioners to request a labeling change from unknown "points of contact" within FDA, U.S. Br. 21, *Buckman* forecloses state-law claims effectively seeking to enforce that duty. As this Court recognized, "The FDCA leaves no doubt that it is the Federal Government rather than private litigants who are authorized to file suit for noncompliance with the [law]: '[A]ll such proceedings for the enforcement, or to restrain violations, of this chapter shall be by and in the name of the United States.'" 531 U.S. at 349 n.4 (quoting 21 U.S.C. § 337(a) (alteration original)); *id.* at 352 ("[W]e have clear evidence that Congress intended that the [statute] be enforced exclusively by the Federal Government.") (citing § 337(a)).

Indeed, allowing *state-law* claims that petitioners allegedly failed to communicate *with FDA* raises the precise concerns the government expressed (and this

Court adopted) in *Buckman*: that private actions eviscerate FDA's enforcement discretion, by disrupting its ability to determine both *whether* and *how* to pursue alleged violations of the duties companies owe FDA. *Id.* at 349-51. In the government's words, private enforcement would:

> (1) "permit juries in different States to reach judgments that differ from FDA's" about whether companies violated their duties to FDA, and "impose massive liability, when FDA would not find any misconduct";
>
> (2) "distort the penalty scheme established by the statute," by providing remedies Congress withheld; and
>
> (3) "interfere with FDA's discretion to decide which of the statutorily prescribed remedies, if any, to pursue," by allowing juries to "substitute their judgments for FDA's as to the appropriate sanction."

Buckman Br., 2000 WL 1364441, *23-*24 (quotations omitted; citing *Crosby v. National Foreign Trade Council*, 530 U.S. 363, 380 (2000); *San Diego Bldg. Trades Council v. Garmon*, 359 U.S. 236, 247 (1959)); *see also Warner-Lambert* Br., 2007 WL 4218889, *18-*19 ("[T]he FDCA gives FDA 'complete discretion' to pursue those remedies that, in the agency's judgment, best fit a violation.... Awards of damages ... interfere with FDA's determination of the appropriate remedy.") (quoting *Heckler v. Chaney*, 470 U.S. 821, 835 (1985)).

The government again fails to square its current position with its past ones. Instead, it simply asserts that "there is no reason to suppose a conflict between

federal and state law if both demand the same conduct." U.S. Br. 26. But that equally was true in *Buckman* and *Warner-Lambert*, where the state-law claims targeting defendants' communications to FDA fully mirrored federal disclosure requirements. The government nonetheless argued—and *Buckman* agreed—that such claims were preempted because they involved communications *to a federal agency*:

> If federal regulatory agencies are to perform the important functions assigned to them by Congress, they must have the ability to decide, free from hindrances imposed by state law, how best to obtain the information they need and how to sanction those who fail to provide such information.

Buckman Br., 2000 WL 1364441, *18; *see also Buckman*, 531 U.S. at 347-48 ("[P]etitioner's dealings with the FDA [are] prompted by [federal law], and the very subject matter of petitioner's statements [to FDA are] dictated by [it]s provisions.").[5] As in *Wyeth*, the government's "dramatic change in position" divests it of deference. 129 S. Ct. at 1203.

Respondents seek to distinguish *Buckman* by asserting that their "traditional failure-to-warn claims long 'predated the federal enactments in question.'" Resp. Br. 57 (quoting *Buckman*, 531 U.S. at 353). But that simply is not so: As in *Buckman*,

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[5] As for the government's claim that *Buckman* is distinguishable because it involved a "collateral attack" on a prior FDA decision, U.S. Br. at 31, that was the concurrence's view—not the Court's (or the government's). *See Buckman*, 531 U.S. at 354-55 & n.2 (Stevens, J., concurring).

respondents' novel theory hinges on claims that petitioners were obligated to disclose information *to FDA*.[6] Once respondents resort to arguing that petitioners were obligated to communicate *with FDA*, the claims are no longer "independent of the federal statutes that establish federal regulatory agencies and require regulated entities to make certain disclosures to those federal agencies." *Buckman* Br., 2000 WL 1364441, *18. Instead, the federal framework is "a critical element." *Buckman*, 531 U.S. at 353. Federal law thus forecloses respondents' novel theory of liability.

CONCLUSION

The judgments should be reversed.

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[6] Indeed, *Buckman* distinguished *Medtronic, Inc. v. Lohr*, 518 U.S. 470 (1996), and *Silkwood v. Kerr-McGee Corp.*, 464 U.S. 238 (1984), on precisely that ground—noting that neither involved communications to a federal agency, but respectively "arose from the manufacturer's alleged failure to use reasonable care in the production of the product," *Buckman*, 531 U.S. at 352, and "the duty of care owed by the producer of plutonium fuel pins to an employee working in its plant." *Id.*

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SUPPLEMENTAL BRIEF

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ACTAVIS INC.,

Petitioner,

v.

JULIE DEMAHY,

Respondent.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Fifth Circuit

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The Amicus Curiae Brief filed by the United States in *Pliva, Inc. v. Mensing*, No. 09-993, and *Actavis Elizabeth, LLC v. Mensing*, No. 09-1039, demonstrates why this Court should grant certiorari in this case. The United States meticulously explains why a generic drug manufacturer may *not*, absent approval by the Food and Drug Administration (FDA), strengthen a warning to the label of an approved abbreviated new drug application (ANDA), even if it has additional information to support such a revision. Contrary to the holding of the Fifth Circuit below, "FDA has consistently taken the position that an ANDA holder may not unilaterally change its approved labeling." Brief for the United States as Amicus Curiae (US Br.) 13.

ARGUMENT

THE COURT SHOULD GRANT REVIEW NOW TO PREVENT SERIOUS HARM TO THE GENERIC DRUG INDUSTRY.

As the United States demonstrates, the numerous federal courts that have addressed preemption of claims against generic drug companies since *Wyeth v. Levine*, 129 S.Ct. 1187 (2009), have incorrectly disregarded the critical differences between the regulatory regimes governing generic and brand drug manufacturers. In particular, as the United States explains, the Fifth Circuit's holding in this case that "the CBE process was available to an ANDA holder to make a unilateral change in its

approved labeling . . . misunderstands FDA's regulations." U.S. Br. 22 n.10. This purely legal issue – whether generic companies may add a warning to their label without FDA approval – is ripe for review, and review by the Court of this discrete issue could prevent potentially hundreds of verdicts against generic drug companies, and the ensuing harm to the supply of low-cost generic drugs.[1]

It is significant that the United States has rejected all of the key arguments that Respondent made to the Fifth Circuit. *First*, the United States states that "[t]he holder of an approved ANDA is not free to change its approved labeling at will." US Br. 12. In contrast the Fifth Circuit held that Actavis could have used the CBE process to unilaterally change its label. App. 23a-33a. *Second*, the United States informs the Court that the prior approval supplement (PAS) process "also was not expressly available to petitioners to make the labeling change respondent seems to envision." US Br. 14-15. Again, the Fifth Circuit held the PAS process was available to generic manufacturers. App. 33a-34a. *Third*, rejecting Respondent's argument, the United States agrees with the Fifth Circuit that Actavis could not have used Dear Doctor Letters to convey a new

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[1] Petitioner has been informed that there are more than 30 federal and 850 state metoclopramide cases pending across the country in which a generic drug company is a defendant. It is likely that there are hundreds or thousands of additional cases pending against generic drug companies where plaintiffs are asserting that under *Wyeth* a generic company had the obligation to unilaterally add a warning to the label on one of its products.

warning that FDA had not approved for its label. US Br. 17-18; App. 34a-35a.

The Government's position that a different theory of liability may be viable is not a reason to defer review of a decision that is clearly wrong and will disrupt a vital industry. Although it recognizes that requiring generic drug companies to replicate the research capabilities of brand drug makers would raise preemption issues (because that would conflict with the low production cost model underlying the Hatch-Waxman Act), the United States leaves room for a claim that a generic company should have used an informal process at FDA to request a labeling change based on published literature, articles which undoubtedly were available to FDA, and the adverse reaction reports that generic companies routinely file with FDA. *See* US Br. 21-22. Such a claim – even if it were viable under the law of a particular state and the necessary elements of causation could be proved – would be very different from the claims that would be allowed under the Fifth Circuit's decision. Trials of the claims actually before the courts in the Fifth Circuit and across the country will waste the resources of the courts and the parties, and litigation of these claims will pose a threat to the generic drug industry until this Court intercedes.

In addition to the district courts in the Fifth Circuit which will be required to follow their Circuit Court's incorrect ruling on the CBE issue,[2] district

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[2] We have identified 23 metoclopramide cases pending in district courts in the Fifth Circuit. There are undoubtedly

courts in other circuits have frequently cited the Fourth Circuit's decision in *Foster v. American Home Products Corp.*, 29 F.3d 165, 170 (4th Cir. 1994), which also incorrectly found that generic drug companies can be held liable for not unilaterally adding new safety information to a drug label.[3] We have also identified 11 district court decisions that have held that a generic drug company can be held liable for not unilaterally changing its label,[4]

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many other failure to warn cases pending against generic drug manufacturers in district courts in that Circuit. All these courts are bound by the Circuit Court's decision in *Demahy*.

[3] Although the statement in *Foster* that generic drug manufacturers "are also permitted to add or strengthen warnings . . . even without prior FDA approval," 29 F.3d at 170, is dicta, it has been followed in four reported decisions and undoubtedly in numerous unreported decisions. *See Dorsett v. Sandoz, Inc.*, 699 F. Supp. 2d 1142, 1162 (C.D. Cal. 2010); *Vitatoe v. Mylan Pharms., Inc.*, 696 F. Supp. 2d 599, 613 (N.D.W. Va. 2010); *Munroe v. Barr Labs., Inc.*, 670 F. Supp. 2d 1299, 1302-03 (N.D. Fla. 2009); *Bartlett v. Mut. Pharm. Co.*, 659 F. Supp. 2d 279, 298 (D.N.H. 2009).

[4] *In re Rudeprion XL Mktg. & Sales Litig.*, No. 09-md-2107, 2010 WL 2135625, at *5, 11 (E.D. Pa. May 26, 2010); *Finnicum v. Wyeth, Inc.*, No. 1:09-CV-785, at 8-9, 11 (E.D. Tex. May 25, 2010) (unreported); *Dorsett*, 699 F. Supp. 2d at 1161-62; *Mosley v. Wyeth, Inc.*, No. 09-0284-KD-C, at 17-18 (S.D. Ala. Jan. 25, 2010) (unreported); *Levine v. Wyeth, Inc.*, No. 8:09-cv-854-T-33AEP, at 11-12 (M.D. Fla. Dec. 8, 2009) (unreported) (magistrate opinion adopted by district court on Jan. 14, 2010); *Munroe*, 670 F. Supp.2d at 1302-03; *Bartlett*, 659 F. Supp. 2d at 296, 299-300; *Stacel v. Teva Pharms., USA*, 620 F. Supp. 2d 899, 907 (N.D. Ill. 2009); *Kellogg v. Wyeth, Inc.*, 612 F. Supp. 2d 421, 431 (D. Vt. 2008); *Barnhill v. Teva Pharms. USA, Inc.*, No. 06-0282-CB-M, 2007 WL 6947996, at *3-5 (S.D. Ala. Apr. 24, 2007),

contrary to the law as explained in our petition and in the United States' amicus brief. Unless this Court resolves this issue now, there could be dozens or even hundreds of additional misguided district court and appellate court decisions, which will impose a significant and unnecessary burden on the generic drug industry.

The United States states that "imposing on a generic manufacturer a state law duty not to market its product without developing for itself knowledge as comprehensive as FDA's or the NDA holder's could pose preemption questions" because it would affect the availability of generic drugs, which would be contrary to the low-cost model envisioned by Hatch-Waxman. *See* US Br. 22. Similarly, the potential costs to the generic drug companies of defending hundreds and possibly thousands of product liability cases before there is a split in the circuits and resolution of such a split by this Court is itself inconsistent with the underlying Hatch-Waxman model of fostering the availability of generic drugs and supports granting certiorari in this action.

The United States argues that the Court should not grant certiorari in *Mensing* because the case is before the Supreme Court in an interlocutory posture and because there is no split in the circuit courts of appeals. Whatever the merits of that argument as applied to *Mensing*, it does not justify

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Louisure-Rodke v. Par Pharm., Inc., No. C03-365RSM, 2006 WL 901657, at *4 (W.D. Wash. Mar. 29, 2006). Three of these decisions also cited *Foster*. *See* note 3, *supra*.

denial of certiorari in the instant case. In contrast to *Mensing*, where the Eighth Circuit did not rule on the core issue of whether a generic company may unilaterally change its label, in the instant case the Fifth Circuit squarely addressed that issue. There is no reason to await the development of trial records when, for the reasons explained in the United States' brief, the legal error is already apparent. And, although a circuit split would furnish an additional reason to grant review, here the widespread misapplication of *Wyeth* together with the severe consequences of delaying review furnish a strong justification for granting review of the pure legal issue that Petitioner has submitted for resolution.

CONCLUSION

In conclusion, the petition for certiorari should be granted.[5]

Respectfully submitted,

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[5] If the Court decides not to schedule this case for briefing and argument, Petitioner respectfully requests that the Court grant the petition, vacate the judgment below and remand for further consideration in light of the views of the United States.

AMICUS CURIAE BRIEF

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Nos. 09-993, 09-1039 and 09-1501

In the Supreme Court of the United States

PLIVA, INC., ET AL., PETITIONERS

v.

GLADYS MENSING

ACTAVIS ELIZABETH, LLC, PETITIONER

v.

GLADYS MENSING

ACTAVIS, INC., PETITIONER

v.

JULIE DEMAHY

ON WRITS OF CERTIORARI TO THE UNITED STATES COURTS OF APPEALS FOR THE FIFTH AND EIGHTH CIRCUITS

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE SUPPORTING RESPONDENTS

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QUESTION PRESENTED

Whether federal law preempts state law causes of action based on a claim that a generic drug approved by the Food and Drug Administration was inadequately labeled.

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ON WRITS OF CERTIORARI
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FOR THE FIFTH AND EIGHTH CIRCUITS

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE SUPPORTING RESPONDENTS

INTEREST OF THE UNITED STATES

These cases concern the circumstances in which state law may hold the manufacturer of a generic drug approved by the Food and Drug Administration (FDA) liable for failing to warn of hazards associated with the drug. At the Court's invitation, the United States filed a brief at the petition stage of two of these cases.

STATEMENT

Petitioners manufactured the generic prescription drug metoclopramide. Respondents sued petitioners alleging, *inter alia*, that they were injured because petitioners failed to adequately warn that long-term use of that drug could cause tardive dyskinesia. The question presented is whether federal law governing generic drug labeling preempts respondents' failure-to-warn claims under state law.

1. FDA regulates the manufacture, sale, and labeling of prescription drugs under the Federal Food, Drug and Cosmetic Act (FDCA), as amended, 21 U.S.C. 301 *et seq.* FDA is charged with ensuring that drugs in commerce are safe and effective under the conditions prescribed, recommended, or suggested in the labeling, 21 U.S.C. 355(d), 393(b)(2)(B), and that they are not misbranded, 21 U.S.C. 321(n), 331(a), (b) and (k), 352. FDA must approve a drug before it is introduced into commerce. 21 U.S.C. 355(a).

a. To obtain approval to market a new drug, a manufacturer must submit a new drug application (NDA) to FDA. 21 U.S.C. 355(b). The NDA must contain, *inter alia*, scientific data and other information demonstrating that the drug is safe and effective, a statement of the drug's components, and specimens of proposed labeling for the drug. 21 U.S.C. 355(b)(1). To be approved, the NDA must show, *inter alia*, that the "drug is safe for use," and "will have the effect it purports or is represented to have[,] under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof." 21 U.S.C. 355(d)(1) and (5). Moreover, in reviewing an NDA, FDA considers evidence submitted by the applicant, and other relevant scientific information,

to determine whether the proposed labeling is accurate, truthful, not misleading, and adequate. Thus, FDA's approval of an NDA includes approval of the proposed labeling. See 21 U.S.C. 355(b)(1)(F) and (d); 21 C.F.R. 314.105(c) and .125(b)(8). A drug approved under the NDA process is often referred to as a "brand-name" drug.

Once a brand-name drug's NDA has been approved and officially listed as such by FDA (see 21 U.S.C. 355(j)(7)), and subject to certain periods of NDA exclusivity (see 21 U.S.C. 355(j)(5)(F)), any manufacturer may seek approval to market a generic version under the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585, known as the Hatch-Waxman Amendments. Those Amendments prescribe a process for submitting an abbreviated new drug application (ANDA) for a generic drug. 21 U.S.C. 355(j). The ANDA approval process for a generic drug does not require the manufacturer to provide independent clinical evidence of safety or efficacy. Instead, the ANDA must generally show, *inter alia*, that the generic drug has the same active ingredient(s) as, and is bioequivalent to, a reference listed drug (RLD), *i.e.*, the brand-name drug to which the proposed generic will be equivalent. 21 U.S.C. 355(j)(2)(A)(ii) and (iv).

The FDCA requires a manufacturer to show that the "labeling proposed for the [generic] drug is the same as the labeling approved for" the RLD. 21 U.S.C. 355(j)(2)(A)(v); see also 21 U.S.C. 355(j)(4)(G). An ANDA therefore must include a comparison of the proposed labeling to the RLD's labeling, 21 C.F.R. 314.94(a)(8)(iv), and a "statement that the applicant's

proposed labeling * * * is the same as the labeling of the [RLD]," 21 C.F.R. 314.94(a)(8)(iii); see 21 C.F.R. 314.105(c). This requirement reflects the fundamental premise of the ANDA process that a generic drug can be relied upon as a therapeutic equivalent of its RLD. See 54 Fed. Reg. 28,884 (1989) (Section 355(j) is intended "to ensure the marketing of generic drugs that are as safe and effective as their brand-name counterparts."). Accordingly, FDA places "a very high priority [on] assuring consistency in labeling," so as "to minimize any cause for confusion among health care professionals and consumers as well as to preclude a basis for lack of confidence in the equivalency of generic versus brand name products." Division of Generic Drugs, FDA, *Policy and Procedure Guide* 37 (1989); see 57 Fed. Reg. 17,961 (1992).

b. A drug is "misbranded" in violation of the FDCA when its labeling is false or misleading, or does not provide adequate directions for use and adequate warnings. See 21 U.S.C. 321(n), 331(a), (b) and (k), 352(a), (f) and (j). The term "labeling" under the FDCA is expansive: It embraces "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." 21 U.S.C. 321(m). Under that definition, "[o]ne article or thing is accompanied by another when it supplements or explains it * * *. No physical attachment one to the other is necessary." *Kordel* v. *United States*, 335 U.S. 345, 350 (1948); see 21 C.F.R. 202.1(*l*)(2). Some labeling—for example, the package insert and other proposed labeling submitted in an NDA under 21 U.S.C. 355(b)(1)—requires FDA's approval and is thus referred to as "approved labeling." Other labeling—for example,

promotional materials and some communications by manufacturers to physicians—does not require such approval, although it must be consistent with the drug's approved labeling, 21 C.F.R. 201.100(d)(1), and a copy must be supplied to FDA for review, 21 C.F.R. 314.81(b)(3)(i).

The labeling of a prescription drug satisfies federal requirements if it gives physicians and pharmacists sufficient information—including indications for use and "any relevant hazards, contraindications, side effects, and precautions"—to allow those professionals to "use the drug safely and for the purposes for which it is intended." 21 C.F.R. 201.100(c)(1). FDA regulations further establish specific requirements for any prescription drug labeling that "purports to furnish information for use," "whether or not [the information] is on or within a package from which the drug is to be dispensed [or] distributed." 21 C.F.R. 201.100(d). Among those requirements is warning language that "shall describe serious adverse reactions and potential safety hazards [and] limitations in use imposed by them." 21 C.F.R. 201.57(e) (2001); see 21 C.F.R. 201.100(d)(3).[1]

c. Information on the risks and benefits associated with a drug may accumulate over time. Accordingly, NDA and ANDA holders must keep records of clinical experiences and ensure that their drugs remain safe and

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[1] In 2006—after the events in *Mensing* (see J.A. 180-181) and very late in the events in *Demahy* (see J.A. 434-435)—the labeling regulations were revised. The standards for older drugs, including metoclopramide, are (as relevant here) essentially unchanged, but now appear at 21 C.F.R. 201.56(e) and .80. See 71 Fed. Reg. 3988, 3996 (2006). This brief discusses only older drugs and cites the standards as codified in 2001 and 2002, which is when respondents allege they were first prescribed metoclopramide (J.A. 180, 434).

effective as labeled. See 21 U.S.C. 355(k). In particular, implementing regulations provide that a manufacturer must record and report certain adverse events to FDA, 21 C.F.R. 314.80(a) and (c) (NDA holders); 21 C.F.R. 314.98(a) (ANDA holders),[2] and must also annually report a "summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product" and a "description of actions the applicant has taken or intends to take as a result of this new information." 21 C.F.R. 314.81(b)(2)(i).

A drug's "labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug." 21 C.F.R. 201.57(e) (2001). That regulation implements the FDCA's provision that a drug that lacks "adequate warnings" is misbranded. 21 U.S.C. 352(f)(2); see 44 Fed. Reg. 37,447 (1979) (citing 39 Fed. Reg. 33,229 (1974)).

A manufacturer may proceed to change its approved labeling by filing a "supplemental application" (also

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[2] FDA interprets 21 C.F.R. 314.80, "Postmarketing reporting of adverse drug experiences," to impose requirements upon all sponsors, including ANDA holders. Those requirements cannot be viewed in isolation or selectively applied to ANDA holders, as the PLIVA petitioners assert (Br. 19). To comply with Section 314.80(c)'s reporting requirements, sponsors determine which adverse drug experiences meet the definitions in Section 314.80(a) and should be reported—an exercise that involves some measure of "review" as described in Section 314.80(b). The "scientific literature" and "postmarketing study" provisions in Section 314.80(d) and (e) are not freestanding obligations, but rather specific rules for reporting adverse drug experience information acquired through those channels.

known as a "supplement"). See 21 C.F.R. 314.70 (2001).[3] ANDA holders must "comply with the requirements [applicable to NDA holders] regarding the submission of supplemental applications." 21 C.F.R. 314.97. Supplements are by regulatory definition part of the application. See 21 C.F.R. 314.3(b). Accordingly, any supplement must be approved by FDA, and that approval in general requires that the application as supplemented satisfy all the requirements of the FDCA and FDA's regulations that apply to original applications.

All changes to a drug's approved labeling require FDA's assent. Certain changes require FDA's prior approval, which a manufacturer seeks by submitting a prior approval supplement (PAS). 21 C.F.R. 314.70(b) and (b)(3) (2001). Certain other changes—including changes to approved labeling "[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction"—are brought to FDA's attention "at the time the applicant makes [the] change" through a "changes being effected" (CBE) supplement. 21 C.F.R. 314.70(c) and (c)(2)(i) (2001); see *Wyeth* v. *Levine*, 129 S. Ct. 1187, 1196 (2009). Manufacturers sometimes also disseminate information about their drugs—including updated warnings—through correspondence to health care providers, known as "Dear Health Care Professional" (DHCP) letters. See 21 C.F.R. 200.5 (setting standards

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[3] The bulk of the events in these cases (see J.A. 180-181, 434-435) occurred before the 2004 revision of the supplemental application regulations at 21 C.F.R. 314.70 (see 69 Fed. Reg. 18,764). Accordingly, this brief discusses only the pre-2004 regulations and agency guidance. The parties have not suggested, and we have not identified, anything in the 2004 revision that would materially affect these cases.

for such correspondence). DHCP letters are "labeling" under 21 U.S.C. 321(m) and 21 C.F.R. 202.1(*l*)(2).[4]

2. According to the allegations in respondents' operative complaints, their physicians prescribed Reglan, the brand-name version of metoclopramide, in March 2001 to treat Mensing's diabetic gastroparesis, and in October 2002 to treat Demahy's gastroesophageal reflux disease. Respondents' pharmacists filled those prescriptions with generic metoclopramide sold by one or more petitioners. Respondents each took metoclopramide for several years, and each developed tardive dyskinesia. J.A. 179-182, 433-435.

When respondents first took metoclopramide, Reglan's approved labeling stated that "[t]herapy longer than 12 weeks has not been evaluated and cannot be recommended," and it warned that there was a risk of tardive dyskinesia that was "believed to increase with the duration of treatment and the total cumulative dose." In 2004, FDA approved a request (made by the then-holder of the Reglan NDA) to add a bold-type sentence to the labeling stating: "Therapy should not exceed 12 weeks in duration." In 2009, FDA approved a boxed warning that "[t]reatment with metoclopramide for longer than 12 weeks should be avoided in all but rare cases" because of the risk of tardive dyskinesia.[5]

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[4] Manufacturers also supply information about their drugs for compilations such as the *Physicians' Desk Reference*, a publication mentioned in Demahy's complaint, J.A. 438-439. Such submissions are also labeling, see 21 C.F.R. 202.1(*l*)(2), but because respondents' brief does not discuss them, this brief discusses only DHCP letters.

[5] The quoted language is drawn from the approved Reglan tablet package inserts, available through http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. See also Actavis Br. 8-12 & nn.3-8.

3. Respondents separately sued certain manufacturers of metoclopramide (some of whom are petitioners here) alleging that the metoclopramide each took was defective because petitioners failed to adequately warn of the risks of long-term use. Mensing contended that "despite mounting evidence [before and during her period of metoclopramide use] that long term metoclopramide use carries a risk of tardive dyskinesia far greater than indicated on the label, no metoclopramide manufacturer took steps to change the label warnings." J.A. 402 (court of appeals' opinion). Her amended complaint alleges that petitioners "[f]ailed to [a]ct as [r]equired by the FDA" with respect to the labeling of their drugs, and that "the package insert for * * * metoclopramide substantially understated the prevalence of acute and long term side effects of ingesting the drug," J.A. 192, 194.

Similarly, Demahy contended that Actavis, Inc. "ignored scientific and medical literature establishing a higher risk of developing tardive dyskinesia [than suggested by its drug's labeling], failed to request a labeling revision from the FDA, failed to change the label itself * * *, and failed to report safety information directly to the medical community." J.A. 522 (court of appeals' opinion). Her amended complaint alleges Actavis, Inc. "failed to fully, truthfully and accurately disclose * * * metoclopramide data to the FDA," and that "the package insert * * * for Reglan did not adequately inform physicians about the risks associated with * * * metoclopramide," J.A. 437, 439.

As relevant here, petitioners moved to dismiss or for summary judgment. The *Mensing* district court granted the motions, holding that failure-to-warn claims

were preempted. J.A. 364-399. The *Demahy* district court denied the motion, holding that failure-to-warn claims could proceed, except "to the extent [they] constitute[] a fraud-on-the-FDA claim" preempted under *Buckman Co.* v. *Plaintiffs' Legal Comm.*, 531 U.S. 341, 348 (2001). J.A. 477-519. It certified its order for interlocutory appeal under 28 U.S.C. 1292(b). J.A. 424.

4. The courts of appeals, addressing largely identical preemption arguments advanced by petitioners, held that respondents' failure-to-warn claims could proceed.[6] J.A. 400-421, 520-563.

Countering petitioners' defense that federal law made it impossible for them to alter their drugs' labeling, respondents offered three mechanisms by which petitioners could have satisfied their state law duty to warn consistent with the FDCA and FDA regulations. Respondents first argued that petitioners could have changed their approved labeling using the CBE process. The *Demahy* court concluded that the CBE process was available to Actavis, Inc., just as it was to the NDA holder in *Wyeth*, based on the court's belief that FDA's regulations requiring "that a generic's label initially conform to the [RLD's label] * * * do not address post-approval modifications at all." J.A. 535; see J.A. 542-551. The *Mensing* court declined to decide whether the CBE process was available to petitioners. See J.A. 412.

Respondents also argued that petitioners could have sent warning DHCP letters or sought FDA's approval to change their approved labeling using the PAS pro-

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[6] Demahy did not appeal the district court's decision regarding the fraud-on-the-FDA aspect of her claim, so that determination is not before this Court.

cess. Both courts of appeals agreed that petitioners could have sought a change through the PAS process, see J.A. 412, 551-552, or asked FDA to coordinate a DHCP letter, see J.A. 413 & n.5, 552-553, while recognizing it would have been inappropriate for petitioners to send such letters on their own, *ibid.* Both courts of appeals also rejected petitioners' argument that uncertainty about what action FDA might have taken in response to such requests was a reason to bar liability. In their view, *Wyeth* "made it clear * * * that uncertainty about the FDA's response * * * makes federal preemption less likely," because "[t]o support preemption [petitioners] must show the likelihood of FDA *in*action." J.A. 414-415; accord J.A. 555-556. Each court found no evidence in the record before it suggesting FDA would have rejected a labeling proposal from petitioners. J.A. 415, 556.

The courts of appeals also rejected petitioners' arguments that permitting state law failure-to-warn claims would unacceptably frustrate the Hatch-Waxman Amendments' purpose of encouraging development of low-cost generic drugs. J.A. 416-418, 557-562. The courts explained that Congress did not intend the Hatch-Waxman Amendments to override "the fundamental requirement of the FDCA that all marketed drugs remain safe." J.A. 417; accord J.A. 561.

SUMMARY OF ARGUMENT

Petitioners contend they could not deliver whatever additional warnings state law required while remaining faithful to FDA's labeling regulations and the Hatch-Waxman Amendments' requirement that a generic drug's approved labeling be the "same as" the brand-name drug's approved labeling. They further claim that

any approach that reconciles state and federal law would impermissibly intrude on FDA's authority. They therefore conclude that respondents' claims must be preempted.

That reasoning is incorrect. FDA regulations require NDA holders and ANDA holders alike to act upon new safety information that warrants added or strengthened warnings. Petitioners are correct that, in meeting that federal duty, they could not properly have invoked the CBE or PAS process, or sent the sort of DHCP letter respondents envision. But ANDA holders nonetheless "should provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised." 57 Fed. Reg. at 17,961.

In particular, a drug is misbranded under the FDCA if "its labeling [does not] bear[] * * * adequate warnings * * * against unsafe dosage or methods or duration of administration or application." 21 U.S.C. 352(f)(2). FDA in turn imposes on manufacturers a duty that a prescription drug's approved "labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug." 21 C.F.R 201.57(e) (2001). This reflects the "central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times." *Wyeth*, 129 S. Ct. at 1197-1198. When Section 201.57(e) obligates an applicant to revise its label, and both generic and brand-name drugs are affected, it is appropriate to assume that FDA (once informed of the relevant new information) will pursue an orderly process to ensure appropriate changes are made.

The question for preemption purposes, therefore, is whether the generic drugs respondents took were misbranded under 21 U.S.C. 352(f)(2) and the standard in 21 C.F.R 201.57(e) (2001). That approach reconciles the Hatch-Waxman Amendments' "same as" requirement with the FDCA's misbranding standard and FDA's implementing regulation. It fulfills Congress's intention that failure-to-warn suits would "provide[] appropriate [compensatory] relief for injured consumers" and "motivat[e] manufacturers * * * to give adequate warnings. *Wyeth*, 129 S. Ct. at 1199-1200. And it avoids the inconsistency in petitioners' position, under which individuals harmed by inadequately labeled generic drugs would have no remedy against the manufacturer, while individuals who took the same drug with the same labeling in its brand-name form would (by virtue of *Wyeth*) have such a remedy.

Those considerations lose force, however, if the drugs were not misbranded under federal law. Moreover, even if an ANDA holder had proposed a labeling change in that situation, FDA would not have engaged with the RLD sponsor to revise its labeling. At this stage of the case, however, assuming the truth of respondents' allegations—which effectively plead that petitioners' drugs were misbranded and that the Section 201.57(e) duty was triggered—respondents' cases should be allowed to proceed.

ARGUMENT

RESPONDENTS' FAILURE-TO-WARN CLAIMS ARE NOT CATEGORICALLY PREEMPTED

A state tort claim is preempted if it is impossible for a plaintiff to comply with both the state law duty underlying the claim and federal regulatory requirements.

Wyeth, 129 S. Ct. at 1196. Even if compliance with both state and federal law is not impossible, the state-law duty underlying a tort claim is preempted if it would frustrate the purposes and objectives of federal statutes and regulations. See *Williamson* v. *Mazda Motor of Am., Inc.*, No. 08-1314, slip op. 5 (Feb. 23, 2011); *Wyeth*, 129 S. Ct. at 1199. "[T]he purpose of Congress is the ultimate touchstone in every pre-emption case." *Wyeth*, 129 S. Ct. at 1194 (quoting *Medtronic, Inc.* v. *Lohr*, 518 U.S. 470, 485 (1996)).

Petitioners contend that because federal law required them to maintain labeling for their generic drugs that was the same as the labeling of the RLD, they cannot be held liable for failing to warn respondents about the risks of long-term metoclopramide use (beyond the warnings already approved for the RLD). Petitioners' argument fails to take account of the substantive and procedural framework under the FDCA and FDA's implementing provisions for revising labeling to reflect associations between a drug and a serious hazard. ANDA holders, like NDA holders, have a duty under federal law to propose appropriate changes to approved labeling to communicate warnings about serious drug hazards. When that duty is triggered, and the ANDA holder does not act upon it, the plaintiff's claim is not preempted.

A. Petitioners Could Have Sought Changes To Their Drugs' Approved Labeling Under The Circumstances Alleged By Respondents

As respondents point out (Br. 22), petitioners now "concede that they could have asked FDA to approve stronger warnings for both Reglan and generic metoclopramide." Respondents continue to suggest, however,

that petitioners could also have used certain FDA regulations to revised their approved labeling in ways the agency does not recognize as permissible. The courts below similarly offered their own interpretations of FDA's regulations that FDA has since informed this Court are mistaken. See Gov't Pet. Stage Amicus Br. 12-18, 22 n.10. In summary, petitioners could not properly have invoked the CBE or PAS process, or sent the sort of DHCP letter respondents envision. But an ANDA holder nonetheless should have provided FDA with new information about risks. This Court will "defer to [FDA's] interpretation of its own regulation[s] * * * unless that interpretation is 'plainly erroneous or inconsistent with the regulation[s].'" *Chase Bank USA, N.A. v. McCoy*, 131 S. Ct. 871, 880 (2011) (citing *Auer v. Robbins*, 519 U.S. 452, 461 (1997)); see *Chevron U.S.A. Inc. v. NRDC*, 467 U.S. 837, 842-843 (1984).

a. The CBE process was not available to petitioners to unilaterally change their drugs' approved labeling. FDA's CBE regulation does apply to ANDA holders. See 21 C.F.R. 314.97. But ANDA supplements are subject to the substantive standards governing ANDAs, so the CBE regulation must be read in conjunction with FDA's regulations pertaining specifically to ANDAs. Those regulations require a generic drug's proposed labeling to be "the same as the labeling of the [RLD]." 21 C.F.R 314.94(a)(8)(iii); see 21 U.S.C. 355(j)(4)(G); 21 C.F.R. 314.150(b)(10) (ANDA approval may be withdrawn if the drug's approved labeling "is no longer consistent with that for the [RLD]"). As a result, the CBE supplement that respondents say petitioners should have filed—to revise the approved labeling on their products alone—would not have satisfied 21 C.F.R.

314.94(a)(8)(iii)'s "same as" requirement, and therefore would not have been approvable.[7]

The Fifth Circuit's error in *Demahy* with respect to CBE changes traces to its mistaken belief that FDA's regulations requiring "that a generic's label initially conform to the [RLD's label] * * * do not address post-approval modifications at all." J.A. 535; see J.A. 542-551. That is incorrect; supplements are by definition part of the application, see 21 C.F.R. 314.3(b), and therefore must (in combination with the application) satisfy the substantive standards for applications.[8]

Indeed, FDA has consistently taken the position that an ANDA holder may not unilaterally change its approved labeling. For example, in promulgating its final rule implementing labeling requirements for ANDAs, FDA rejected the suggestion that the regulations should permit generic manufacturers to deviate from the brand-name labeling "to add contraindications, warnings, precautions, adverse reactions, and other safety-related information." 57 Fed. Reg. at 17,961.

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[7] Contrary to respondents' contention (Br. 33-34), the neighboring exception in 21 C.F.R. 314.94(a)(8)(iv) permitting proposed ANDA labeling to differ from the RLD's approved labeling "to comply with current FDA labeling guidelines or other guidance" does not apply on the facts alleged here. That regulation addresses the narrow situation where FDA itself has specifically "require[d] a change in the labeling of a drug product to make available important new information about the safe use of a drug product, but the [RLD's] labeling has not yet been updated to reflect this change." 54 Fed. Reg. at 28,884. There was no such action on FDA's initiative in the period relevant to these cases.

[8] By contrast a CBE supplement is the appropriate process for an ANDA holder to conform its approved labeling to updated RLD approved labeling because, under those circumstances, the change would be consistent with the substantive requirements for generic labeling.

FDA explained that "[e]xcept for labeling differences due to [issues not relevant here], the ANDA product's labeling must be the same as the listed drug product's labeling because the listed drug product is the basis for ANDA approval." *Ibid.* FDA stated instead that an ANDA holder wishing to add a warning should furnish adequate supporting information to FDA, which would then determine whether the labeling for all drugs should be modified. *Ibid.*; see pp. 19-21, *infra*. FDA's guidance on labeling changes reiterates that limitation on changes to an ANDA. Center for Drug Evaluation & Research, *Guidance for Industry: Changes to an Approved NDA or ANDA* 24 (Nov. 1999).

b. The PAS process also was not available to petitioners to make the labeling change respondents envision. As relevant here, the PAS process applied to "change[s] in labeling, except one described in paragraph[] (c)(2) * * * of this section." 21 C.F.R. 314.70(b)(3)(i) (2001). That exception is a cross-reference to the CBE provision for added or strengthened warnings, which respondents say describes the labeling change that petitioners should have made here. See, *e.g.*, Resp. Br. 31. Such changes could therefore not appropriately be made through the PAS process. Moreover, 21 C.F.R 314.94(a)(8)(iii)'s "same as" requirement would prevent approval of a PAS proposing labeling that would diverge from the RLD's approved labeling.

Respondents' reading (Br. 32) of 21 C.F.R. 314.70(b)(3)(i) (2001)—that it simply acknowledges the possibility of a CBE change without ruling out the possibility of a PAS change—may also be linguistically plausible. But FDA does not interpret its regulation that way; rather, FDA's stated approach (see pp. 19-21, *in-*

fra) is that ANDA holders should contact FDA under a less formalized process so that it can pursue orderly changes for all affected drugs. That said, FDA would not have ignored the substantive labeling changes proposed in such a PAS on procedural grounds. Rather, FDA would have construed such a supplement as a request to determine whether the labeling for the RLD and all generic equivalents should be revised.

c. Respondents also argue (Br. 36-37) that petitioners could have sent a DHCP letter to respondents' physicians warning of risks greater than those described in petitioners' drugs' approved labeling. To be sure, nothing in the FDCA or FDA's regulations categorically forbids an ANDA holder from unilaterally sending a DHCP letter. And a DHCP letter can be an appropriate way to bring new information to the attention of medical professionals. But the particular letter respondents envision would only be appropriate in tandem with a corresponding change to the drug's approved labeling. A DHCP letter was not the freestanding option respondents portray it to be.

A DHCP letter is "labeling" under the FDCA and FDA's regulations, 21 C.F.R. 202.1(*l*)(2), so the manufacturer must provide a copy to FDA, 21 C.F.R. 314.81(b)(3), which will review the letter for compliance with the FDCA and FDA regulations governing matters such as misbranding. See Center for Drug Evaluation & Research, *Manual of Policies & Procedures* 6020.10 (July 2, 2003) (*MAPP*) (establishing protocols for internal FDA review and monitoring of such correspondence).

The DHCP letter respondents envision would have been subject to 21 C.F.R. 201.100(d), which addresses

prescription drug labeling "that furnishes * * * information for use" of the drug. Such labeling must be "consistent with and not contrary to [the drug's] approved * * * labeling." 21 C.F.R. 201.100(d)(1). The DHCP letter respondents envision would have violated that provision because its very purpose would have been to depart from what respondents allege was an insufficiently serious warning in the approved labeling about metoclopramide's long-term risks. Cf. *FDA, Guidance for Industry: Presenting Risk Information in Prescription Drug and Medical Device Promotion* 2 n.5 (Draft May 2009) (strongly advising against issuing promotional labeling that includes risk information "not in the product's approved labeling or appropriate for inclusion in the labeling").[9]

In addition, under 21 C.F.R. 314.150(b)(3), FDA may withdraw approval of an ANDA if "the labeling of the drug"—which, again, includes DHCP letters—"based on a fair evaluation of all material facts, is * * * misleading in any particular." Depending on its content, a DHCP letter from an ANDA holder could inaccurately imply therapeutic differences between the generic drug and its RLD that do not exist, and therefore be misleading.

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[9] Strictly speaking, 21 C.F.R. 201.100 establishes not absolute requirements for prescription drugs, but rather an exemption from otherwise applicable statutory requirements. It implements 21 U.S.C. 352(f), which provides that a drug is misbranded "[u]nless its labeling bears * * * adequate directions for use," but further provides that FDA shall exempt a drug from that condition when it is "not necessary for the protection of the public health." Prescription drugs (for which directions for use are supplied by physicians and pharmacists) are exempted, provided they meet the conditions of 21 C.F.R. 201.100.

d. Even though pursuing the avenues described above would not have been appropriate, petitioners were nonetheless obligated (accepting respondents' allegations as true) to seek to revise their labeling and provide FDA with supporting information about risks. FDA contemplated this situation. In the preamble to the final rule implementing the ANDA application process, it explained how ANDA holders should discharge their duty to provide adequate warnings:

> If an ANDA applicant believes new safety information should be added to a product's labeling, it should contact FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised. After approval of an ANDA, if an ANDA holder believes that new safety information should be added, it should provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised.

57 Fed. Reg. at 17,961. This approach gives FDA the opportunity to use its authority to pursue an orderly process to reconcile what could otherwise be conflicting statutory mandates that a generic drug not be misbranded, 21 U.S.C. 352, yet also bear labeling "the same as the labeling approved for the [RLD]," 21 U.S.C. 355(j)(4)(G).[10]

Situations where an ANDA holder alone has a basis to believe stronger warnings should be added to its

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[10] Respondents suggest (Br. 35-36) the same result could be accomplished by filing a citizen petition under 21 C.F.R. 10.30. Although not FDA's preferred procedure, FDA would not refuse to entertain such a petition.

drug's approved labeling have not been known to arise frequently. And when one does, there tend to be unique, fact-specific considerations; as the parties and several amici point out, the Hatch-Waxman Amendments have fostered a diverse marketplace for generic drugs. For that and other reasons, FDA has not promulgated a formal regulation for this process. Instead, the agency has chosen to make available to generic manufacturers points of contact in FDA's Office of Generic Drugs, just as it does for any number of potential issues not specifically provided for by formal regulation. FDA's internal procedures recognize that "some labeling reviews" will require the Office of Generic Drugs to consult other FDA components with particular expertise, such as the Office of Review Management (now known as the Office of New Drugs). *MAPP* 5200.6, at 1 (May 9, 2001); see *id.* at 5 (FDA request-for-consultation form applicable to "labeling revision"). In that process, intra-agency consultations regarding "ANDAs with possible serious safety concerns" are assigned the highest priority. *Id.* at 3.

Thus, had a metoclopramide ANDA holder provided information to FDA at the time of the events in this case, FDA would have used intra-agency consultations to subject any serious safety concerns to a substantive evaluation like that for a supplement under 21 C.F.R. 314.70, and taken action as appropriate. At the time of the events in this case, FDA could have requested (though not directly required) the NDA holder to make appropriate changes to its approved labeling. Had the NDA holder refused, FDA could have withdrawn approval of the application, see 21 U.S.C. 355(e); 21 C.F.R. 314.150(a)(2)—most obviously because the NDA holder's

approved labeling, like the ANDA holder's, would have been inadequate in light of the new information.[11]

B. A State Failure-To-Warn Claim Is Not Preempted When A Manufacturer Has A Federal Duty To Propose A Corresponding Change To Approved Labeling But Fails To Do So

In *Wyeth*, the plaintiff contended (and a state jury agreed) that she sustained injuries caused by Phenergan, a brand-name drug sold by the defendant manufacturer (Wyeth), and that her injuries were proximately caused by inadequate warnings in Phenergan's approved labeling. See 129 S. Ct. 1192-1193. This Court rejected Wyeth's impossibility preemption defense. It read the record to reflect newly acquired information on Wyeth's part regarding the risk of gangrene from administration of Phenergan. *Id.* at 1196-1197. That understanding of the record was the basis for two conclusions: First, Wyeth could have appropriately invoked the CBE process to change Phenergan's approved labeling. See *id.* at 1197. Second, in light of Wyeth's duty "to revise its label 'to include a warning as soon as there is reasonable evidence of an association of a serious hazard with [its] drug,'" the Court concluded that "when the [gangrene] risk * * * became apparent, Wyeth had a duty to provide a warning that adequately described

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[11] FDA now has authority under the Food and Drug Administration Amendments Act of 2007 (FDAAA), Pub. L. No. 110-85, 121 Stat. 823, to require labeling changes based on new information from a variety of sources. See 21 U.S.C. 355(o)(4) (Supp. III 2009). FDA is currently developing guidance on how that authority will be exercised for changes to NDA and ANDA approved labeling. The existence of that authority and FDA's implementation of it could affect the preemption analysis of cases like these arising from events occurring after FDAAA's enactment.

that risk." *Id.* at 1198 (quoting 21 C.F.R. 201.80(e) (formerly 21 C.F.R. 201.57(e) (2001))).

Taking respondents' allegations as true, petitioners were under the same duty as Wyeth "to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug." 21 C.F.R. 201.57(e) (2001). And they had been directed to "provide adequate supporting information" for FDA to "determine whether the labeling for the generic and listed drugs should be revised." 57 Fed. Reg. at 17,961.

1. A generic drug manufacturer must seek to revise its drug's approved labeling to include a warning as soon as there is reasonable evidence of an association of a serious hazard with the drug

A drug is misbranded under the FDCA if, *inter alia*, "its labeling [does not] bear[] * * * adequate warnings * * * against unsafe dosage or methods or duration of administration or application." 21 U.S.C. 352(f)(2). As a corollary, a drug is also misbranded if "it is dangerous to health when used in the dosage or manner, or with the frequency or duration prescribed, recommended, or suggested in the labeling." 21 U.S.C. 352(j). A misbranded drug may not be introduced into commerce. See 21 U.S.C. 331(a).

To implement Section 352, FDA requires that a section of a prescription drug's approved labeling headed "Warnings" describe "serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur." 21 C.F.R. 201.57(e) (2001); see 44 Fed. Reg. at 37,447 (citing 39 Fed. Reg. at 33,229) (describing authority for 21 C.F.R. 201.57(e) (2001)). That same regulation imposes a duty to keep warnings current: "The labeling

shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved." 21 C.F.R 201.57(e) (2001). This duty applies to NDA holders and ANDA holders alike. "Reasonable evidence" under the regulation, FDA has explained, is evidence "on the basis of which experts qualified by scientific training and experience can reasonably conclude that the hazard is associated with the use of the drug." 44 Fed. Reg. at 37,447. An "association" between a drug and a serious hazard exists "when there is significant medical evidence of a possible health hazard"; labeling must be revised "without waiting for a causal relationship to be established by definitive studies." 39 Fed. Reg. at 33,231 (referenced by 44 Fed. Reg. at 37,447).

As this Court recognized in *Wyeth*, that duty to keep warnings current reflects the "central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. It is charged both with crafting an adequate label and with ensuring that its warnings remain accurate." 129 S. Ct. at 1197-1198 (citing, *inter alia*, 21 C.F.R. 201.80(e) (formerly 21 C.F.R. 201.57(e) (2001)).

When Section 201.57(e) obligates an applicant to revise its label, it may properly be assumed that FDA will permit an appropriate change to discharge that duty.[12]

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[12] There are, infrequently, situations where a revision arguably called for by the standard in Section 201.57(e) must be reconciled with other risk communication considerations. Cf. *Dowhal* v. *SmithKline Beecham Consumer Healthcare*, 88 P.3d 1 (Cal. 2004) (addressing FDA's decision regarding labeling of nicotine-containing smoking-cessation products, which required balancing warnings to pregnant women about the products' potential reproductive hazards against, *inter alia*, the risk that such warnings would misleadingly suggest that continuing to

Indeed, it would be both paradoxical and contrary to FDA's statutory responsibilities for FDA to insist upon a labeling revision under a certain standard—"reasonable evidence of an association of a serious hazard with a drug," *ibid.*—and then fail to respond positively to a warning proposed in conformity with that standard.[13]

2. *A generic drug manufacturer's federal duty to seek a labeling revision supplies the appropriate standard for the preemption inquiry here*

Drugs with FDA approval are presumptively lawful to sell in commerce. Respondents do not contend otherwise or suggest that petitioners' drugs simply should not have been available on the market. Because respondents' claims are directed only to the labeling of petition-

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smoke was a safer course). The parties do not suggest these cases raise such a situation.

[13] *Wyeth* addressed both the manufacturer's duty to revise its approved labeling and FDA's hypothetical response to a proposed revision, but it treated them as distinct issues. See 129 S. Ct. 1198-1199. The issue of FDA's hypothetical response was the subject of minimal briefing—it was raised only in Wyeth's reply brief. See Pet. Reply Br. at 12, *Wyeth*, *supra*, No. 06-1249. Nonetheless, this Court's discrete discussion of FDA's hypothetical response has led many lower courts to take the question of preemption in this context to turn on whether "FDA would not have approved a change to [the drug's] label." *E.g.*, J.A. 556 (brackets in original) (quoting *Wyeth*, 129 S. Ct. at 1198).

The circumstances of *Wyeth* did not, however, require a direct focus on the likelihood of FDA disapproval. If under FDA regulations "Wyeth had a duty to provide a warning that adequately described [the relevant] risk," *Wyeth*, 129 S. Ct. at 1198, then those facts required it to act on the duty and FDA's procedures gave Wyeth the means to do so. Wyeth, therefore, did not find itself in an impossible situation calling for preemption. In those circumstances, the Court understandably insisted upon "clear evidence" before it could "credit Wyeth's contention that the FDA would have prevented it from adding a stronger warning." *Id.* at 1198-1199.

ers' drugs, the preemption question presented turns on the extent to which state law may impose a duty to warn without conflicting with federal law.

At the most basic level, there is no reason to suppose a conflict between federal and state law if both demand the same conduct from the defendant. When, as here, federal law requires a manufacturer to act to update its labeling, a State may impose a similar duty and consequent damages liability for failing to meet that duty. Cf. *Riegel* v. *Medtronic, Inc.*, 552 U.S. 312, 330 (2008) (analogous conclusion in context of an express preemption clause); *Bates* v. *Dow Agroscis. LLC*, 544 U.S. 431, 447-448 (2005) (same); *Lohr*, 518 U.S. at 495 (same).

That framework for generic drugs is in harmony with *Wyeth*'s rule for brand-name drugs: Irrespective of whether a drug is approved under an NDA or an ANDA, if the drug was misbranded due to new safety information not reflected in its labeling, then the plaintiff's claims are not preempted. The manufacturer was under a federal duty to revise its federally approved labeling and FDA gave it the ability to seek such changes. Petitioners, by contrast, argue that they enjoy a free pass accorded to virtually no other manufacturer regarding product labeling—in the field of drugs or otherwise. Individuals harmed by inadequately labeled generic drugs would (on petitioners' view) have no remedy against the manufacturer, while individuals who took the same drug with the same labeling in its brand-name form would (by virtue of *Wyeth*) have such a remedy. "If Congress had intended to deprive injured parties of a long available form of compensation"—and to do so in such an inconsistent manner—"it surely would have ex-

pressed that intent more clearly." *Bates*, 544 U.S. at 449.

Focusing the preemption inquiry on the standard in 21 C.F.R. 201.57(e) (2001) to avoid misbranding accommodates a number of potentially contradictory commands from the FDCA, FDA's regulations, and this Court's decisions:

- It respects both the Hatch-Waxman Amendments' requirement that the approved labeling of a generic drug be the "same as" the RLD's labeling, 21 U.S.C. 355(j)(2)(A)(v), and FDA's regulation that implements the FDCA's misbranding provision by requiring approved labeling to be revised "as soon as there is reasonable evidence of an association of a serious hazard with a drug," 21 C.F.R. 201.57(e) (2001).
- It appropriately presumes that FDA, if confronted with new safety information triggering the duty FDA itself set out in Section 201.57(e), would act on that information in the way FDA itself indicated it would in its 1992 preamble, see 57 Fed. Reg. at 17,961. See *United States* v. *Chemical Found.*, 272 U.S. 1, 14 (1926) ("The presumption of regularity supports the official acts of public officers.").
- It remains faithful to the principle that "[f]ailure-to-warn actions, in particular, lend force to the FDCA's premise that manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times," and thus "state law offers an additional, and important, layer of consumer

protection that complements FDA regulation." *Wyeth*, 129 S. Ct. at 1202-1203.

- It preserves an appropriate ambit for "widely available state rights of action [to] provide[] appropriate relief for injured consumers," because there is generally no "federal [compensatory] remedy for consumers harmed by unsafe or ineffective drugs." *Wyeth*, 129 S. Ct. at 1199.
- It functions as a measured incentive for drug manufacturers to bring new safety information to FDA's attention. See *Wyeth*, 129 S. Ct. at 1200 ("[S]tate-law remedies further consumer protection by motivating manufacturers * * * to give adequate warnings.").[14]

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[14] Some of petitioners' amici (Apotex Amicus Br. 26-30; Generic Pharm. Ass'n Amicus Br. 10-15; Morton Grove Amicus Br. 28-31), and even some petitioners at the petition stage (see 09-993 Pet. 20-22; 09-1039 Pet. 10-11) have touched on a distinct but related preemption question: to what extent do the Hatch-Waxman Amendments permit state law to impose a duty on a generic manufacturer to acquire or develop safety information about its drugs? In the extreme (*e.g.*, by requiring clinical trials), such a duty could undermine the viability of the generic pharmaceutical market the Hatch-Waxman Amendments sought to foster. But that would pose preemption questions different from the ones respondents' complaints more directly raise. Respondents' primary theory appears to be that information already in petitioners' possession (see J.A. 198-199, 438-439, 441, 444) or readily available in published scientific literature (see J.A. 193, 439, 441) showed that the labeling was inadequate. Petitioners (see 09-993 Pet. 21) and their amici (see Morton Grove Amicus Br. 28-29) disagree with that as a factual matter, suggesting a far broader knowledge base would have been necessary. Even respondents' complaints could be read to support that view. See J.A. 193 (alleging petitioners "failed to investigate"); J.A. 439 (referring to petitioners' "ability to review data from clinical studies"). But given these cases' interlocutory posture, this

Those principles lose force, however, if the generic drug is not misbranded and the duty in Section 201.57(e) is not triggered. In that event, there is no federal policy against selling the drug and no call to change its label (let alone for FDA to orchestrate a change to the RLD's label). There is diminished value, from the perspective of federal law, to the incentives created by a state tort duty for a manufacturer to propose a warning that federal law would not require. And if the generic drug and RLD are not misbranded, then petitioners' plea to impossibility becomes more substantial: Even if the ANDA holder proposed a labeling change, FDA would not engage with the RLD sponsor to revise its labeling; yet without such a change, the ANDA holder would be obliged to maintain approved labeling the "same as" the RLD's approved labeling.[15]

3. Accepting respondents' allegations as true, petitioners were under a federal duty to revise their approved labeling

In the posture of these cases, this Court must accept respondents' allegations as true. They contend that accumulating scientific evidence established that the risk of tardive dyskinesia (unquestionably a serious hazard) associated with long-term use of metoclopramide was significantly greater than what was reflected in petition-

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Court should accept as true respondents' allegations that information known by or readily available to petitioners warranted a labeling change.

[15] Because this case concerns only generic drugs, it is not necessary to consider whether the preemption analysis would be different in a case brought (like *Wyeth*) against an NDA holder with access to the CBE process, but involving (unlike *Wyeth*) a drug for which a revised warning was not required by Section 201.57(e) to avoid misbranding.

ers' drug's approved labeling. See p. 9, *supra*. In addition to whatever claim those allegations state under state law, they would also establish that petitioners' metoclopramide products were misbranded under 21 U.S.C. 352(f)(2) because those drugs would lack adequate warnings, and petitioners would have failed to discharge their duty under Section 201.57(e) to seek a revision to their approved labeling in light of newly acquired information not previously considered by FDA. Accordingly, petitioners' preemption defense cannot prevail at the pleadings stage—though, of course, it may ultimately succeed if petitioners can show the true facts are otherwise.

4. Petitioners' arguments for preemption of respondents' claims are not persuasive

Petitioners offer several arguments why FDA's role in mediating ANDA-initiated changes to approved labeling supports their position that failure-to-warn claims against ANDA holders are either categorically preempted or impose a special burden on plaintiffs. None is persuasive.

a. The PLIVA petitioners' primary submission is that "speculation about how FDA would have responded to a hypothetical submission seeking warning changes" would "'usurp[] a function that Congress has assigned to a federal regulatory body.'" PLIVA Br. 49-50 (quoting *Arkansas La. Gas Co.* v. *Hall*, 453 U.S. 571, 580-582 (1981) (*Arkla*), and citing *Nantahala Power & Light Co.* v. *Thornburg*, 476 U.S. 953 (1986); *Chicago & N.W. Transp. Co.* v. *Kalo Brick & Tile Co.*, 450 U.S. 311 (1981)). The PLIVA petitioners err because the decisions they cite rest on the extraordinarily comprehensive authority the agencies in question had in their re-

spective fields: "[The Federal Energy Regulatory Commission has] plenary authority over interstate wholesale rates, and * * * the States [may] not interfere with this authority." *Nantahala*, 476 U.S. at 966; accord *Arkla*, 453 U.S. at 580; see *Kalo Brick & Tile*, 450 U.S. at 326 ("Because Congress granted the exclusive discretion * * * to the [Interstate Commerce] Commission, there is no further role that the state court could play."). A central "consideration[] underlying the [filed rate] doctrine" applied in those cases is "preservation of the agency's primary jurisdiction over reasonableness of rates." *Arkla*, 453 U.S. at 577-578 (citation omitted); accord *Kalo Brick & Tile*, 450 U.S. at 325. By contrast, "Congress did not intend FDA oversight to be the exclusive means of ensuring drug safety and effectiveness." *Wyeth*, 129 S. Ct. at 1200. Rather, "the FDCA's premise [is] that manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times," and thus "state law offers an additional, and important, layer of consumer protection that complements FDA regulation." *Id.* at 1202-1203.

The PLIVA petitioners further contend (Br. 5) that their reading of *Arkla*, *Nantahala*, and *Kalo Brick & Tile* mirrors the United States' reading of those cases in a prior submission to this Court. See U.S. Br. at 20-21, *Warner-Lambert Co.* v. *Kent*, 552 U.S. 440 (2008) (U.S. *Warner-Lambert* Br.). That brief was, however, filed without the benefit of this Court's decision in *Wyeth*. Moreover, the fraud-on-the-FDA issues in *Warner-Lambert* and *Buckman*, *supra*, impermissibly intruded on federal law because they constituted a collateral attack on a decision actually made by FDA in the past—thus they entailed "second-guessing * * *

FDA's decisionmaking" on an issue actually presented to it and "a difficult inquiry into [the] counterfactual situation" that would have existed absent the alleged fraud. U.S. *Warner-Lambert* Br. 20 (internal quotation marks omitted). By contrast, the appropriate inquiry here addresses whether petitioners' drugs violated substantive misbranding and regulatory standards based on new information not presented to FDA.

If FDA had actually rejected a labeling change proposed by an ANDA holder, the cases petitioners cite might well operate to bar a jury from revisiting FDA's decision. But because here the matter was not even presented to FDA, and "the statute contemplates that federal juries will resolve most misbranding claims," *Wyeth*, 129 S. Ct. at 1197, a court and jury should not be prevented from deciding an issue of misbranding in the course of adjudicating a tort suit.[16]

b. Petitioners also contend (PLIVA Br. 50-53; Actavis Br. 28-29) that FDA's response to a hypothetical warning proposal would be part of the causal chain respondents would have the burden of establishing in their cases-in-chief under state law. Respondents disagree. Br. 41-44. This Court need not, and should not, resolve that issue of state law because the lower courts did not pass upon it, and because it is beyond the scope of the question presented, which addresses only the extent of federal preemption.

Federal law demands only that the ANDA holder be allowed to raise as an affirmative defense under federal law the issue of whether its drug was not misbranded. That approach comports with settled federal preemption

[16] A misbranding determination in a private tort suit would not, of course, bind FDA in the exercise of its regulatory authority.

law and background tort principles. A defendant ordinarily bears the burden of proving the circumstances supporting its preemption defense. See *Wyeth*, 129 S. Ct. at 1196; *CSX Transp., Inc.* v. *Easterwood*, 507 U.S. 658, 670 (1993) ("[The tort defendant] has failed to establish that the regulations apply to these cases, and hence we find [plaintiff's claim] is not preempted.").

This approach is also practical. A tort plaintiff's failure-to-warn claim necessarily entails some showing of deficiency in labeling—an unreasonable warning in a negligence claim, or an inadequate warning in a strict liability claim. The thrust of such claims is likely to resemble the FDCA's standard for misbranding and FDA's interpretation of that standard, see pp. 23-25, *supra*. Thus, if a plaintiff succeeds in proving her claim under state law, there is at least some reason to believe the drug was misbranded and federal law demanded revised labeling—and the defendant can fairly be tasked with showing otherwise.

c. The Actavis petitioners also criticize (Br. 29-31) as impermissibly speculative any approach that would attempt to account for how FDA would have responded to a hypothetical warning proposal. Other petitioners express concern (PLIVA Br. 55-61) that allowing litigation over FDA's response to a hypothetical warning proposal would overburden FDA with requests for documents and testimony, or encourage excessive defensive submissions by ANDA holders to FDA. But the approach to preemption in this brief turns on whether the substantive standard in Section 201.57(e) and the FDCA's misbranding provisions were violated, not on what FDA would have done in response to a proposed

labeling change—although evidence of the latter could be relevant. The concerns about speculation over FDA's response and burdens on FDA's resources are therefore significantly diminished.

In addition, the United States' position is that records and employees of the federal government are immune from third-party subpoenas issued in private litigation, and that such records and testimony must be sought under an agency's Touhy regulations, see generally *United States ex rel. Touhy* v. *Ragen*, 340 U.S. 462 (1951), subject only to deferential judicial review under the Administrative Procedure Act, 5 U.S.C. 706(2)(A). That is, to be sure, no guarantee against intrusion. See U.S. *Warner-Lambert* Br. at 22-23. But the United States expressed that concern in *Wyeth*, see U.S. *Wyeth* Br. at 24, and this Court evidently rejected it. Moreover, this Office has been informed that, in the two years since *Wyeth* was decided, FDA has actually seen *fewer* attempts to obtain its records through third-party subpoenas. In light of that experience, FDA would expect a similarly modest burden from an inquiry in tort litigation into misbranding.

FDA is likewise not prepared to predict that a ruling in respondents' favor would unreasonably encourage ANDA holders to inundate the agency with proposed warning revisions with the expectation that FDA would reject them, perhaps with preemptive effect. Naturally, FDA would not condone that practice. *Wyeth* created a similar incentive for NDA holders, but in FDA's experience thus far it has not unleashed a surge of defensive CBE supplements.[17] As a practical matter, genuinely

[17] Under current regulations a CBE change to strengthen a warning need not be effected prior to FDA's approval of the supplement. See

new information about drugs in long use (as generic drugs typically are) appears infrequently, so the risk of overwhelming FDA seems attenuated in this setting. And if trivial submissions became a problem, FDA could promulgate regulations to manage the information flow.

CONCLUSION

The judgments of the courts of appeals should be affirmed.

Respectfully submitted.

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21 C.F.R. 314.70(c)(6) (2010). Thus, neither an NDA holder nor an ANDA holder need ever invest in implementing an unapproved change.

AMICUS CURIAE BRIEF

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In The Supreme Court of The United States

PLIVA, INC., *ET AL.*, *Petitioners*,
v.
GLADYS MENSING, *Respondent*.

ACTAVIS ELIZABETH LLC, *Petitioner*,
v.
GLADYS MENSING, *Respondent*.

ACTAVIS INC., *Petitioner*,
v.
JULIE DEMAHY, *Respondent*.

On Writs of Certiorari to the United States Courts of Appeals for the Eighth Circuit and for the Fifth Circuit

BRIEF FOR ADMINISTRATIVE LAW AND CIVIL PROCEDURE SCHOLARS AS *AMICI CURIAE* IN SUPPORT OF RESPONDENTS

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INTEREST OF *AMICI CURIAE*

Amici are scholars who teach and write about civil procedure and federal preemption of state law.[1] We file this brief to address the relationship between preemption doctrine and procedural rules. The arguments made by petitioners and their *amici* blur this relationship and obscure the traditional role that preemption plays in the adjudicative process. *Amici* write to clarify the basic principle that federal preemption of a state-law tort claim is a defense that must be pled and proven by the defendant. Reaffirming this principle is appropriate as a matter of preemption law, basic pleading doctrine, and this Court's longstanding precedent regarding the scope of jurisdiction under 28 U.S.C. § 1331.

Our scholarly interest in preemption and procedure arises from teaching and writing in a variety of related fields, including constitutional law, administrative law, and civil procedure. Edward J. Brunet is the Henry J. Casey Professor of Law at Lewis & Clark Law School where he teaches Civil Procedure. William W. Buzbee is a Professor of Law at Emory University School of Law, where he teaches Administrative Law. Robert L. Glicksman is the J.B. and Maurice C. Shapiro Professor of

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[1] Counsel for all parties have consented to the filing of this brief, and those consents are on file with the Clerk of the Court. Pursuant to Rule 37.6, *amici* affirm that no counsel for a party authored this brief in whole or in part, that no such counsel or party made a monetary contribution to the preparation or submission of this brief, and that no person other than *amici* and their counsel made such a monetary contribution.

Environmental Law at George Washington University Law School where he teaches Administrative Law. Thomas O. McGarity holds the Joe R. and Teresa Lozano Long Endowed Chair in Administrative Law at the University of Texas, where he teaches Environmental Law and Torts. Nina A. Mendelson is a Professor of Law at the University of Michigan Law School, where she teaches Administrative Law and Environmental Law. Alexander A. Reinert is an Associate Professor of Law at the Benjamin N. Cardozo School of Law, where he teaches Civil Procedure and Constitutional Law. Sidney Shapiro is the University Chair in Law at Wake Forest University School of Law, where he teaches Administrative Law. Adam Steinman is a Professor of Law at Seton Hall University School of Law, where he teaches Civil Procedure.

SUMMARY OF ARGUMENT

Preemption doctrine is typically associated with substantive federalism concerns. It serves to demarcate the boundaries of state and federal enforcement power, encouraging federal actors to speak clearly when invading the police powers traditionally reserved to the States, thereby ensuring that principles of federalism are maintained as much as possible in favor of State autonomy. This case, however, implicates the procedural dimensions of preemption doctrine. It presents the difficult question of the proper role for a court resolving a preemption defense at the motion to dismiss stage.

Petitioners and their *amici* maintain that plaintiffs in a state law tort action must plead facts establishing an absence of preemption before proceeding past the motion to dismiss stage.[2] *See* Br. for Pet'rs Pliva *et al.* 29 (arguing that to prove causation, respondents must prove that FDA "would have exercised its exclusive authority to implement the suggested warnings in a timely fashion."); *id.* 50 (terming FDA's "independent action" an "essential element in the causal chain"); Br. for Pet'rs Actavis *et al.* 17 (treating FDA action as causal element); *id.* 28-29; Br. for *Amici Curiae* Morton Grove Pharm., Inc. *et al.* 26-27 (arguing that FDA action is critical to causation and burden rests on respondents). Absent such pleading, they suggest, the plaintiff has failed to state a claim for relief. *See, e.g.*, Br. for Pet'rs Pliva *et al.* 51-52; Br. for Pet'rs Activa *et al.* 28-29; Br. for *Amici Curiae* Morton Grove Pharm., Inc. *et al.* 26-27. Although petitioners and their *amici* are less than clear regarding the source of this rule, their argument implies that plaintiffs are obliged to plead and prove a negative – the non-existence of preemption – even though this Court and lower federal courts have consistently treated preemption as an affirmative defense. Petitioners' suggestion is inconsistent with basic pleading

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[2] Actavis and Pliva filed motions to dismiss in the *Mensing* case, *see Mensing v. Wyeth, Inc.*, 588 F.3d 603, 605 (8th Cir. 2009), and Actavis filed a motion to dismiss in *Demahy*, *see Demahy v. Actavis, Inc.*, 593 F.3d 428, 430 (5th Cir. 2010). Although other defendants below filed motions styled as motions for summary judgment, these were made on legal, not factual grounds. *See* Br. for Resp'ts. 5 & n.4. Thus, as a practical matter, the cases below were resolved at the motion to dismiss stage.

doctrine, ignores the presumption against preemption, and would undermine the delicate balance of federal subject matter jurisdiction that this Court has maintained for nearly a century.

If the argument by petitioners and their *amici* were accepted, it would create irreconcilable tension in various strands of this Court's preemption jurisprudence. Indeed, petitioners and their *amici* disregard the equilibrium that this Court has struck through its preemption jurisprudence. The longstanding presumption against preemption, reaffirmed only two years ago in *Wyeth v. Levine*, 129 S. Ct. 1187 (2009), forms the backdrop for important aspects of both pleading jurisprudence and subject matter jurisdiction principles that would be substantially undermined by the arguments of petitioners and their *amici*. On the question most directly implicated in this case, the presumption against preemption explains precisely why preemption is an affirmative defense that a plaintiff need not anticipate to state a claim for relief at the motion to dismiss stage. Indeed, when this Court has considered the relationship between pleading and preemption it has consistently held that preemption is only considered after a plaintiff's complaint has stated a claim for relief. *See Franchise Tax Board of California v. Construction Laborers Vacation Trust*, 463 U.S. 1, 13-14 (1983). Moreover, the presumption mandates that the defendant show that a particular state law action is preempted by federal law. At the motion to dismiss stage, the defendant can only do so by showing an entitlement to dismissal on preemption grounds

based on the allegations that appear on the face of the complaint. Here, the complaint cannot be read to support a defense of preemption on its face.

The coherence of this approach is only amplified when one turns to consider subject matter jurisdiction, where the presence of a putative preemption defense has never been the basis for federal subject matter jurisdiction, except for narrow exceptions not applicable here, because it is not considered part of the plaintiff's "well pleaded complaint." *See Louisville & Nashville R. Co. v. Mottley*, 211 U.S. 149 (1908) (articulating rule). If petitioners are correct that facts necessary to rebut preemption must be pleaded and proved by the plaintiff, some actions in which preemption is a potential defense would arguably "arise under" federal law, permitting the exercise of federal subject matter jurisdiction under 28 U.S.C. § 1331. Decades of case law has established the opposite proposition – the presence of affirmative defenses with federal roots, like preemption, is insufficient to justify the exercise of "arising under" jurisdiction. In sum, pleading principles establish that a plaintiff is not expected to anticipate the defense of preemption in the pleadings; principles of federal subject matter jurisdiction go further, by labeling as "artful pleading" a plaintiff's attempt to incorporate preemption issues into her complaint.

Petitioners and their *amici* are indifferent to this finely calibrated approach, insisting that the possibility of a preemption defense creates a need for a plaintiff to incorporate facts rebutting preemption

into her cause of action. Thus, under petitioners' version, the presumption against preemption has no weight and the normal pleading rules regarding affirmative defenses are inapplicable. Moreover, if this Court accepts petitioners' argument, federal subject matter jurisdiction could be appropriate in any state-law case that touches on a conceivable federal regulatory concern that might cause a defendant to raise preemption as an affirmative defense. In addition, by proposing that the potential for preemption creates additional elements for a state law cause of action that must be pleaded by the plaintiff, petitioners and their *amici* misunderstand the elements of a plaintiff's failure to warn claim and the nature of the causation inquiry. For all of these reasons, the arguments made by petitioners and their *amici* should be rejected and the decisions below affirmed.

ARGUMENT

I. Respondents Need Not Anticipate the Affirmative Defense of Preemption in Their Pleadings

A. Petitioners' Argument Is Undermined By Basic Pleading Rules

To understand the conflict between petitioners' argument and well-established pleading principles, it is necessary to connect some of the assumptions that go unstated in petitioners' briefing. First, *Wyeth* made clear that one key issue in

determining whether state failure to warn claims are preempted in the drug labeling context is whether the FDA would have rejected more stringent warnings had the manufacturer sought its approval for the warnings. 129 S. Ct. at 1197-98. Second, *Wyeth* also clarified that the party seeking to invoke preemption had the burden of showing that the agency would not have approved such warnings, even had additional information been provided justifying the new warnings. *Id.* at 1196-98 (referring to Wyeth's "burden" to establish preemption and its failure to provide "clear evidence" that the FDA would have rejected a proposed warning). Petitioners and their *amici*, however, suggest that it is respondents who must show that the agency would have acted had it been provided with the critical information, because it is incorporated into the element of causation in plaintiffs' tort claims. *See* Br. for Pet'rs Pliva *et al.* 29, 50 (arguing that to prove causation, respondents must show that FDA would have exercised its authority); Br. for Pet'rs Actavis *et al.* 17, 28-29 (same); Br. for Amici Curiae Morton Grove Pharm. *et al.* 26-27 (same). Petitioners and their amici suggest that this case is different because here, unlike in *Wyeth*, a generic drug manufacturer does not have the power to propose unilaterally a labeling change through the "changes being effected" regulations.[3] Therefore, the argument goes, FDA action is more critical here than in *Wyeth*. *See, e.g.*, Br. for Pet'rs Pliva *et al.* 51-52. Accepting for the purposes of argument that this correctly describes the regulatory

[3] 21 C.F.R. § 314.70(c).

regime for generic drug manufacturers, petitioners' contention only goes to the strength of their preemption defense, and not the party that bears the burden regarding preemption. Respondents may be forced to shoulder the burden of pleading and proving how the FDA would have acted only if they also have the burden of disproving preemption. As we discuss below, imposing any such burden on respondents would be inconsistent with rules of pleading and this Court's precedents regarding the allocation of burdens for raising and establishing affirmative defenses.

The Federal Rules of Civil Procedure set forth the circumstances under which a plaintiff's complaint will pass the minimal threshold to discovery. *See* Fed. R. Civ. P. 8(a); 12(b)(6). The Rules provide that affirmative defenses must be set forth in an answer. *See* Fed. R. Civ. P. 8(c)(1). Thus, just as a plaintiff must set forth her claims with a "short and plain statement," Fed. R. Civ. P. 8(a)(2), the defendant "must . . . state in short and plain terms its defenses to each claim." Fed. R. Civ. P. 8(b)(1)(A). Nearly one hundred years ago, this Court clarified that in the "orderly course, the plaintiffs were required to state their own case in the first instance, and then to deal with the defendants' after it should be disclosed in the answer." *Taylor v. Anderson*, 234 U.S. 74, 75 (1914). The adoption of the Federal Rules did not alter this rule and this Court has consistently "refused to change the Federal Rules governing pleading by requiring the plaintiff to anticipate" an affirmative defense. *Crawford-El v. Britton*, 523 U.S. 574, 595 (1998); *see*

also Jones v. Bock, 549 U.S. 199, 215-16 (2007); *Gomez v. Toledo*, 446 U.S. 635, 639-40 (1980).

The Court has made this division of pleading responsibilities clear in the context of qualified immunity, *Crawford-El*, 523 U.S. at 595, *Gomez*, 446 U.S. at 640, *Siegert v. Gilley*, 500 U.S. 226, 231 (1991), exhaustion of administrative remedies, *Jones*, 549 U.S. at 215-16, statute of limitations, *Zenith Radio Corp. v. Hazeltine Research, Inc.*, 401 U.S. 321, 334 (1971), and most importantly, preemption. *E.g.*, *Wyeth*, 129 S. Ct. at 1196-98; *Hillsborough County, Fla. v. Automated Medical Laboratories, Inc.*, 471 U.S. 707, 716 (1985) (referring to the showing that party seeking to establish preemption must make). Thus, the invocation of preemption *after* a complaint is filed cannot affect the standard by which the sufficiency of a complaint is judged under Rules 8 or 12.

This rule has specific implications when an affirmative defense turns on factual determinations. Most importantly, a plaintiff is not required to plead facts tending to rebut an affirmative defense to defeat a motion to dismiss at the pleading stage. *Jones*, 549 U.S. at 215-16. Nor may a court rely on a factual determination to resolve a motion to dismiss based on an affirmative defense without running afoul of the Seventh Amendment. *See Byrd v. Blue Ridge Rural Elec. Co-op, Inc.*, 356 U.S. 525, 531-32 (1958). In the Title VII context, for instance, an employer may take up the burden of persuading the factfinder that it would have imposed the same adverse employment action on an employee absent

an illicit motive. *See* 42 U.S.C. § 2000e-2(m) (approving of limited liability in mixed-motive cases); *id.* § 2000e-5(g)(2)(B) (requiring an employer to "demonstrat[e] that [it] would have taken the same action in the absence of the impermissible motivating factor" in order to limit its liability to solely declaratory relief, specified injunctive relief, and attorneys' fees and costs). This Court has never suggested, however, that such a defense can be resolved in the ordinary course at the motion to dismiss stage. *Cf. Desert Palace, Inc. v. Costa*, 539 U.S. 90, 98-99 (2003) (holding that plaintiff bears no special burden in mixed motive cases); *Swierkiewicz v. Sorema, N.A.*, 534 U.S. 506, 511-12 (2002) (describing minimal pleading burden for Title VII plaintiffs).

Recognizing that an issue is properly considered an affirmative defense necessarily implies that the party seeking to invoke it bears both the burden of production and persuasion on that issue. *See, e.g., Meacham v. Knolls Atomic Power Laboratory*, 554 U.S. 84 (2008) (holding that exemption from liability for disparate impact claim under ADEA for employer actions based on reasonable factors other than age creates an affirmative defense); *Pennsylvania State Police v. Suders*, 542 U.S. 129, 152 (2004) (noting that plaintiff might "elect to allege facts relevant to mitigation in her pleading . . . but she would do so in anticipation of the employer's affirmative defense, not as a legal requirement").[4] Of course, affirmative

[4] This burden of pleading carries over to evidentiary stages of the case. *See, e.g., Meacham*, 554 U.S. at 101-02 (where

defenses may be dispositive at the motion to dismiss stage, but to do so the entitlement to the defense must be obvious from the face of the complaint. Thus, in *Jones*, *supra*, the Court analogized to the statute of limitations context, observing that if the limitations bar is shown by the allegations of the complaint, dismissal is proper. 549 U.S. at 215. The key point is that "[w]hether a particular ground for opposing a claim may be the basis for dismissal for failure to state a claim depends on *whether the allegations in the complaint suffice to establish that ground*, not on the nature of the ground in the abstract." *Id.* (emphasis added); *see also Leveto v. Lapina*, 258 F.3d 156, 161 (3d Cir. 2001) ("[A] complaint may be subject to dismissal under Rule 12(b)(6) when an affirmative defense ... appears on its face" (internal quotation marks omitted)) (cited with approval by *Jones*, 549 U.S. at 215); *Accord Goodman v. Praxair, Inc.*, 494 F.3d 458, 464 (4th Cir. 2007) (en banc) (affirmative defense may be resolved by Rule 12(b)(6) motion in "the relatively rare circumstances where facts sufficient to rule on an

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exemption from liability is "in the orthodox format of affirmative defense," Court is compelled to hold that defendant must convince factfinder of exemption's applicability); *see also* James Bradley Thayer, A PRELIMINARY TREATISE ON EVIDENCE 368-369 (1898) ("In general, he who seeks to move a court in his favor, whether as an original plaintiff . . . or as a defendant . . . must satisfy the court of the truth and adequacy of the grounds of his claim, both in point of fact and law."). Even in the unusual circumstance in which the plaintiff has better access than the defendant to the information relevant to an affirmative defense, this Court has declined to alter the usual rule of pleading and proof. *See Taylor v. Sturgell*, 553 U.S. 880, 907 (2008).

affirmative defense are alleged in the complaint"); *EPCO Carbon Dioxide Prods., Inc. v. JP Morgan Chase Bank, N.A.*, 467 F.3d 466, 470 (5th Cir. 2006) (defense must appear on face of the complaint); *McKenna v. Wright*, 386 F.3d 432, 436 (2d Cir. 2004) (at motion to dismiss stage, plaintiff is entitled to all reasonable inferences that both support his claim and rebut the affirmative defense); *Jacobs v. City of Chicago*, 215 F.3d 758, 775 (7th Cir. 2000) (Easterbrook, J., concurring in part and concurring in the judgment) (noting that Rule 12(b)(6) is a poor fit for resolving affirmative defenses that are based on factual determinations); 5B WRIGHT & MILLER, FEDERAL PRACTICE AND PROCEDURE: CIVIL 3D § 1357, at 708-10 (2004).

This general observation about affirmative defenses is reflected in this Court's preemption case law. Although this Court has considered preemption defenses at many different procedural stages, it has never dismissed on preemption grounds at the motion to dismiss stage when the defense, as in the instant case, hinges on historical facts that are subject to resolution by a traditional factfinder. At the motion to dismiss stage, preemption can only succeed as a defense when the complaint itself establishes the facts upon which the preemption defense rests. Accordingly, when a preemption defense implicates only legal considerations, as in complete preemption, this Court has not hesitated to resolve such issues at the pleading stage. *See Rush Prudential HMO, Inc. v. Moran*, 536 U.S. 355, 374-375 (2002) (resolving express preemption claim at complaint stage). This Court, however, has yet to

resolve an implied conflict preemption case in favor of the party seeking preemption at the motion to dismiss stage, where a factual inquiry was necessary to determining the existence of preemption. *See Geier v. American Honda Motor Co., Inc.*, 529 U.S. 861, 865 (2000) (decided after summary judgment); *California v. ARC America Corp.*, 490 U.S. 93, 99 (1989) (decided after settlement); *Hillsborough County*, 471 U.S. at 711 (decided after bench trial); *cf. Wyeth*, *supra* 129 S. Ct. at 1193 (decided after jury trial).[5] And many of the express preemption cases have also been resolved at advanced procedural stages. *Medtronic, Inc. v. Lohr*, 518 U.S. 470 (1996) (summary judgment); *Cipollone v. Liggett Group, Inc.*, 505 U.S. 504 (1992) (jury trial); *Fidelity Federal Sav. & Loan Ass'n v. de la Cuesta*, 458 U.S. 141 (1982) (summary judgment).

If there were any doubt upon whom the burden rests in a case like this, it is resolved by *Wyeth*, in which the Court stated it would not find impossibility preemption "absent clear evidence that the FDA would not have approved a change to Phenergan's label." 129 S. Ct. at 1198. That the evidence had to be supplied by Wyeth and not raised at the pleading stage by the injured consumer is

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[5] One case in which the Court resolved preemption on an implied preemption theory at the motion to dismiss stage, *Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341 (2001), is notable both for its application solely to fraud on the FDA claims and for basing its holding solely on legal conclusions, not on any factual dispute. *Id.* at 348-49 (holding that FDCA created "comprehensive scheme" that displaced state law); *id.* at 352 (limiting reach of decision to "fraud-on-the-agency" state law claims).

further confirmed by the Court's emphasis that "Wyeth has offered no such evidence," that it "cannot credit Wyeth's contention that the FDA would have prevented it from adding a stronger warning," and that "Wyeth has failed to demonstrate" an entitlement to the "demanding defense" of impossibility preemption. *Id.* at 1198-99. Similarly, when discussing Wyeth's alternative argument for implied preemption based on a frustration of Congressional purpose, the court found that "Wyeth has not persuaded us that failure-to-warn claims like Levine's obstruct the federal regulation of drug labeling." *Id.* at 1204. Petitioners and their *amici* claim that the instant case is different because here, in contrast to *Wyeth*, any action by the FDA is purely speculative and therefore cannot be established by the plaintiff, but this begs the question of who bears the burden of establishing this element of the preemption defense. As the foregoing discussion makes clear, it is inconsistent with pleading doctrine to place that burden on a plaintiff.[6]

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[6] Consistent with the view that preemption is an affirmative defense, this Court has treated the defense as one that can be waived or forfeited if not raised below, although an appellate court has discretion to consider a late-raised argument. *See Exxon Shipping Co. v. Baker*, 554 U.S. 471, 486-87 (2008) (considering preemption argument even though it had been raised in an untimely manner). The Court has treated preemption as jurisdictional only when the federal law purports to displace entirely state court jurisdiction by providing exclusive federal jurisdiction over the dispute. *See International Longshoremen's Ass'n, AFL-CIO v. Davis*, 476 U.S. 380, 393 (1986).

B. Petitioners' Argument Is In Irreconcilable Tension with Decades of Subject Matter Jurisdiction Jurisprudence

The standard pleading rule imposing on defendants the burden of raising an affirmative defense and not requiring plaintiffs to anticipate such a defense in the complaint is not simply a rule borne of administrative convenience regarding which party is in the best position to plead a particular set of facts. In addition, the Court's subject matter jurisdiction jurisprudence makes clear that the allocation of pleading burdens is necessary to vindicate the federalism concerns that inform the division of jurisdiction between the state and federal systems. This Court has consistently taken these concerns into account by holding that the facts rebutting preemption play no role in the plaintiff's affirmative case. Petitioners pay no heed to this long-standing precedent.

Although the cases at bench are amenable to federal jurisdiction because of diversity of citizenship, petitioners' argument, if accepted, would have radical consequences for "arising under" jurisdiction pursuant to 28 U.S.C. § 1331. The Court has stated multiple times that plaintiffs cannot create federal question subject matter jurisdiction under 28 U.S.C. § 1331 by including as part of their affirmative claim allegations that anticipate the preemption defense – it is a long established application of the "well pleaded complaint rule." *See Caterpillar, Inc. v. Williams*, 482 U.S. 386, 393

(1987) (describing "settled law" that arising under jurisdiction cannot be based on preemption defense); *Franchise Tax Board of California v. Construction Laborers Vacation Trust*, 463 U.S. 1 (1983) (declining to exercise Section 1331 jurisdiction where federal issue only arose through preemption defense); *see also Louisville & Nashville R. Co. v. Mottley*, 211 U.S. 149 (1908) (introducing well-pleaded complaint rule); *Grable & Sons Metal Products, Inc. v. Darue Engineering & Mfg.*, 545 U.S. 308, 315 (2005) (applying well-pleaded complaint rule to quiet title action). Under this Court's rulings, first the plaintiff establishes a claim for relief and then the preemption defense comes into play. *See Franchise Tax Board*, 463 U.S. at 13-14. Accepting petitioners' argument, however, would imply that plaintiffs bringing state tort law claims that implicate preemption defenses would necessarily have to include facts rebutting such defenses to plead their cause of action. To hold that plaintiffs not only may but must plead facts tending to rebut the preemption defense would entirely undermine longstanding case law regarding limited federal subject matter jurisdiction and the Court's refusal to tolerate "artful pleading" to expand subject matter jurisdiction.

It is black letter law that a federal court lacks "arising under" jurisdiction via 28 U.S.C. § 1331 over a claim unless the federal issue is placed on the face of the well-pleaded complaint, as defined by the elements of the cause of action. The rule respects federalism by permitting the state in the first instance to apportion the pleading burden and by

ensuring that the federal courts will remain a limited forum, preventing an influx of state law claims into federal court simply because federal law provides a basis for a particular defense. *See Grable & Sons Metal Products*, 545 U.S. at 313-14 (finding arising under jurisdiction over state law claims "always raises the possibility of upsetting the state-federal line drawn . . . by Congress"); *Healy v. Ratta*, 292 U.S. 263, 270 (1934) (noting that federal jurisdiction is limited because of "[d]ue regard for the rightful independence of state governments"); Arthur R. Miller, *Artful Pleading: A Doctrine in Search of Definition*, 76 TEX. L. REV. 1781, 1783 (1998) ("artful pleading" doctrine respects power of state courts "to articulate and develop their own substantive law even when a federal issue may constitute an ingredient of a case").

This issue has arisen numerous times in the context of the defense of preemption, and the Court has consistently held, with limited exceptions having to do with "complete" preemption, that federal jurisdiction will not turn on whether preemption analysis will play a role in resolving a plaintiff's claim. The case upon which the "well pleaded" complaint rule rests, *Mottley*, is itself a precursor to preemption cases, and confirms that the defense of preemption is not part of the plaintiff's complaint. In *Mottley*, the federal issue that was claimed to form the basis for "arising under" jurisdiction was the plaintiffs' expectation that the defendants would argue that they could not comply with a contract to provide free rail transportation because doing so would directly conflict with a federal statute. 211

U.S. at 150. In other words, *Mottley* was an early example of conflict preemption, and the Court found that jurisdiction was not proper despite the fact that the parties agreed that the construction and validity of the federal law was a critical aspect of the dispute.

More recently, in *Franchise Tax Board*, the Court found that there was no federal subject matter jurisdiction over a California state law claim that the defendants claimed was preempted by ERISA. 463 U.S. at 13-14. California law established the elements of the claim "without reference to federal law" and therefore "federal law becomes relevant only by way of a defense to an obligation created entirely by state law, and then only if appellant has made out a valid claim for relief under state law." *Id.* at 13. This was precisely the situation for which the well-pleaded complaint rule was adopted, despite the fact that all parties agreed that preemption analysis would ultimately resolve the dispute in question. *See id.* at 12; *accord Caterpillar, Inc.*, 482 U.S. at 393.

The Court has articulated only two exceptions to this rule, neither of which applies here. First are those cases in which Congress explicitly provides for jurisdiction over state law claims in federal court, such as in the Price-Anderson Act, 42 U.S.C. § 2014(hh). *See Beneficial Nat. Bank v. Anderson*, 539 U.S. 1, 6 (2003); *El Paso Natural Gas Co. v. Neztsosie*, 526 U.S. 473, 484-485 (1999). There is no basis for finding this exception to apply here. The second exception is when a federal statute completely preempts a state law action; that is

where "federal statutes at issue provide[] the exclusive cause of action for the claim asserted and also set forth procedures and remedies governing that cause of action." *Beneficial Nat. Bank*, 539 U.S. at 8. In this circumstance the state law claim is said to be "recharacterized" as a federal claim, because federal law provides the relevant and exclusive cause of action. *See Metropolitan Life Ins. Co. v. Taylor*, 481 U.S. 58, 64 (1987) (finding that some state tort claims were completely preempted by ERISA); *Avco Corp. v. Aero Lodge No. 735, Intern. Ass'n of Machinists and Aerospace Workers*, 390 U.S. 557, 560-561 (1968) (finding complete preemption of some state law claims by Labor Management Relations Act). It is noteworthy that this Court has applied this recharacterization analysis in only two circumstances, for some claims implicating ERISA and the LMRA. Indeed, the tension between *Franchise Tax Board* and the line of authority that began with *Avco* has been criticized, with some Justices arguing that the *Avco* line is an unwarranted exception to the "well-pleaded complaint rule." *See Beneficial Nat. Bank*, 539 U.S. at 12-13 (Scalia, J., dissenting). In any event, no one maintains here that the FDCA creates a cause of action that displaces the state law failure to warn claims at issue here.

Petitioners' position would thus not only conflict with basic pleading doctrine, it also would turn principles of "arising under" jurisdiction on their head. Accepting petitioners' argument would require plaintiffs not only to anticipate the affirmative defense of preemption in their

complaints, but would actually turn the facts rebutting preemption into an element of the plaintiffs' substantive legal claim. What once was "artful pleading" would now be considered required pleading. Perhaps more troubling, the principles of federalism which call for limited federal subject matter jurisdiction would no longer be operative in the preemption context.

II. The Presumption Against Preemption Squarely Places the Burden of Showing Preemption on Petitioners

The need for defendants to plead and prove their entitlement to a preemption defense is consistent not only with basic rules of pleading and subject matter jurisdiction principles, but it also is the most coherent way to integrate the background presumption against preemption into the pleading context. Although Petitioners' *amici* have questioned whether the presumption against preemption applies here, *see* Br. for *Amici Curiae* Morton Grove Pharm., Inc., *et al.* 18-19, this Court only two years ago reaffirmed the presumption in a similar context. *See Wyeth*, 129 S. Ct. at 1194-95; *see also Lohr*, 518 U.S. at 485. This presumption is particularly applicable in the field of state tort law, including failure to warn claims, where a preemption defense would implicate the "historic police powers of the States." *Wyeth* at 1194-95. Thus, the presumption against preemption operates to require that an important national governmental interest be shown to justify infringing on the traditional state law power to regulate products based on health and

safety concerns. In the field of drug law, then, the presumption against preemption ensures that consumers will be protected as much as possible by their own states' laws, except when it conflicts with a very important national interest.

To the extent that the presumption has ever been called into question, it is in areas that do not implicate federalism concerns, such as fraud-on-the-agency claims. *See Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341, 351-52 (2001) (distinguishing traditional state tort law claims from a fraud-on-the-agency claim). *Wyeth* made this crystal clear when it rejected a similar argument to abandon the presumption against preemption for all implied preemption cases, terming any reliance on *Buckman* "especially curious, as that case involved state-law fraud-on-the-agency claims, and the Court distinguished state regulation of health and safety as matters to which the presumption does apply." 129 S. Ct. at 1195 n.3.

The reason for the presumption against preemption jibes well with the federalism concerns that inform principles of federal subject matter jurisdiction articulated above: absent "the clear and manifest purpose of Congress," this Court will not construe federal acts to override the powers of the State to regulate within its traditional police powers. *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218, 230 (1947). Generally, principles of federalism permit both federal and state authorities to regulate health and safety issues; the question in preemption cases is whether Congress has left room for the States to

operate as they traditionally have. Adhering to the presumption is necessary so that federal activity displaces as little state law as possible. *See* Stephen A. Gardbaum, *The Nature of Preemption*, 79 CORNELL L. REV. 767, 806-07 (1994).

Therefore, if Congress' intent is ambiguous, preemption must be rejected so as to protect state autonomy – to do otherwise "would evade the very procedure for lawmaking on which *Garcia* [*v. San Antonio Metro. Trans. Auth.*, 469 U.S. 528 (1985)] relied to protect states' interests." *Gregory v. Ashcroft*, 501 U.S. 452, 464 (1992) (internal quotation marks omitted). Petitioners and their *amici* would go beyond what was rejected in *Garcia* and *Gregory* – they ask this Court to hold that preemption is available simply because of the failure of plaintiff to plead facts tending to rebut the preemption defense. The procedural requirement that defendants show an entitlement to the preemption defense at the motion to dismiss stage by demonstrating that their entitlement appears on the face of the complaint is therefore the only way to operationalize the presumption against preemption in the pleading context. Any other result would leave state autonomy in the hands of the drafters of a plaintiff's complaints, depriving states of the protection afforded by requiring that Congress clearly indicate its intent to preempt state law claims. Needless to say, this turns the presumption against preemption on its head. Instead of the presumption operating to ensure that those with the most incentive to invoke preemption – regulated entities – plead and prove it, it leaves to individual

plaintiffs the burden of pleading and proving a lack of preemption. It would become a presumption in name only.

III. Petitioners' Reliance on the Element of Causation Cannot be Squared with the Elements of the Claim at Issue

Despite the requirements of pleading and preemption law, petitioners and their *amici* argue that for respondents to plead causation, they must allege the FDA would have approved a request for a more stringent warning had it been provided with relevant information about the safety of Metoclopramide from petitioners. Although petitioners attempt to couch this argument as somehow separate from preemption, for the reasons explained above, this is untenable. To the extent that petitioners seek to argue as a matter of state tort law that such a causation requirement exists, this contention is without merit for several reasons.

First, the question of whether such a requirement exists is solely a function of state substantive law, the content of which is not before this Court. Even so, as a matter of basic tort law in Louisiana and Minnesota, where respondents filed suit, the element of causation requires only that respondents show that but for an inadequate warning they would not have been injured. *Willett v. Baxter Int'l Inc.*, 929 F.2d 1094, 1098 (5th Cir. 1991) (in failure to warn case under Louisiana law, causation is established by showing that relevant decision-maker would have acted differently had an

adequate warning been provided); *Gray v. Badger Min. Corp.*, 676 N.W.2d 268, 276 (Minn. 2004) (holding that causation inquiry in failure to warn cases focuses on whether parties would have acted differently with adequate warning). Indeed, in *Wyeth*, the Court explicitly treated the question of causation – whether the plaintiff's injury would "have occurred if Phenergan's label had included an adequate warning" – to be a matter of tort law, separate from the question of preemption. 129 S. Ct. at 1194 & n.2 ("The dissent's frustration with the jury's verdict does not put the merits of Levine's tort claim before us, nor does it change the question we must decide-whether federal law pre-empts Levine's state-law claims."). Preemption cannot both be an affirmative defense and redefine the elements of a plaintiff's prima facie case. *Meacham*, 554 U.S. at 93; *Public Employees Retirement System of Ohio v. Betts*, 492 U.S. 158, 181 (1989), *superseded by statute on other grounds*, Public Law No. 101-433, 104 Stat. 978 (1990).

Second, to the extent that causation is in dispute, it is not a matter that can be resolved at the pleading stage. Causation is a fact-intensive inquiry that normally is resolved after discovery, at summary judgment or trial. *See, e.g., Coray v. Southern Pac. Co.*, 335 U.S. 520, 523-24 (1949) (finding that issue of proximate cause in negligence case was question for jury); *Garnier v. Rodriguez*, 506 F.3d 22, 27 (1st Cir. 2007); *Bailey v. Floyd County Bd. of Educ. By and Through Towler*, 106 F.3d 135, 145 (6th Cir. 1997). Even in the context of Article III standing, which requires that a plaintiff

prove causation not only as an element of its claim but also to invoke federal jurisdiction, this Court has recognized that at the motion to dismiss stage, "general factual allegations of injury resulting from the defendant's conduct may suffice." *Lujan v. Defenders of Wildlife*, 504 U.S. 555, 561 (1992) (recognizing that at summary judgment, plaintiff will have to put forward more specific evidence to establish standing); *Miccosukee Tribe of Indians of Florida v. Southern Everglades Restoration Alliance*, 304 F.3d 1076, 1081 (11th Cir. 2002) (finding injury-in-fact and causation sufficiently alleged at motion to dismiss stage)

Petitioners and their *amici* imply that preemption is required here not only because plaintiffs cannot show that the FDA would have approved more stringent warnings had it been provided with additional information, but also because even making the inquiry into what the FDA would have done conflicts with federal authority over drug regulation because it invites speculation about federal decisionmaking. *See* Br. of Petr's Pliva, *et al.* 53-55; Br. of *Amici Curiae* Morton Grove Pharm., Inc. *et al.* 27-28. Thus, the argument goes, focusing on the counterfactual question about what the FDA would or would not have done itself interferes with federal law and calls for preemption here. This argument is without merit. When one recognizes that the burden of establishing preemption falls on the party seeking to invoke the defense, it is clear that requiring regulated entities to show that the FDA would not have acted actually assists federal regulation. This rule puts the incentive to provide

information to the FDA on the proper parties – the regulated entities – thus ensuring that the FDA is regulating with the full slate of available information. *See Wyeth*, 129 S. Ct. at 1202 (noting FDA's limited resources and incentive provided by state tort actions). The alternative would leave the FDA in the position of regulating the field alone, with regulated entities having little to no incentive to provide new information to improve the quality of regulation. *See id.* at 1202-03 & n. 12; *Bates v. Dow Agrosciences LLC*, 544 U.S. 431, 451-52 (2005) (noting that state law tort claims tend to reinforce agency regulation); Thomas O. McGarity, THE PREEMPTION WAR 1-17 (2008) (detailing Vioxx's regulatory history and the withholding of relevant safety data from the FDA).

This Court's decision in *Arkansas Louisiana Gas Co. v. Hall*, 453 U.S. 571 (1981) (*Arkla*), is not to the contrary. There the claim itself – not a defense – rested on a proposition about what the Federal Energy Regulatory Commission would have done had respondents sought a change in the contract price for natural gas. *Id.* at 574. Moreover, in *Arkla*, FERC had taken a formal position in opposition to respondents' claim and the operative statute directly conflicted with the basis for respondent's affirmative claim. *Id.* at 579-80. Finally, it is instructive that the respondents were a regulated entity in *Arkla* – thus the Court's decision operated to place on the *Arkla* respondents the same incentive that properly is placed on petitioners here: to cooperate with and provide new information to the relevant regulatory agency.

CONCLUSION

For the reasons set forth above and in respondents' brief, *amici* respectfully urge the Court to affirm the judgments below.

Respectfully submitted,

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PLIVA, INC., ET AL.,

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v.

GLADYS MENSING,

Respondent.

ACTAVIS ELIZABETH L.L.C.,

Petitioner,

v.

GLADYS MENSING,

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ACTAVIS INC.,

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v.

JULIE DEMAHY,

Respondent.

ON WRITS OF CERTIORARI TO THE UNITED STATES COURTS OF APPEALS FOR THE EIGHTH CIRCUIT AND FOR THE FIFTH CIRCUIT

BRIEF OF THE AMERICAN ASSOCIATION FOR JUSTICE AS AMICUS CURIAE SUPPORTING RESPONDENTS

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INTEREST OF AMICUS CURIAE

The American Association for Justice ("AAJ"), formerly the Association of Trial Lawyers of America, respectfully submits this brief as *amicus curiae* in support of Respondents. This brief is filed with the consent of all parties.[1]

AAJ is a voluntary national bar association whose trial lawyer members primarily represent individual plaintiffs in personal injury cases and other civil actions, including products liability cases. Throughout its history, AAJ has advocated in courts, in state legislatures, and in Congress to preserve the fundamental protections afforded by state tort law and to ensure that state tort claims provide injured persons with effective legal recourse and remedies. By bringing such claims on behalf of people injured by pharmaceutical drugs and by testifying before Congress about the Food, Drug, and Cosmetic Act and the need to ensure the safety of pharmaceutical drugs manufactured for the public, AAJ's members have helped to ensure that the nation's consumers have access to safe and effective pharmaceuticals.

SUMMARY OF ARGUMENT

The law of preemption has become a continuing tug-of-war between the states and the federal government. Indeed, this tug-of-war is a concerted, targeted, and protracted effort on behalf of the pharmaceutical industry

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1. Letters of consent from both parties have been filed with the Clerk of Court. Pursuant to *Rule* 37.6, *amicus* states that no counsel for a party authored any part of this brief, nor did any person or entity other than amicus, its members, or its counsel make a monetary contribution to its preparation or submission.

to promote their business interests, namely financial gain, while escaping liability and accountability for their tortious conduct resulting in injury or death to the American people.

Fundamental principles of federalism are at the heart of this case. Following lengthy and spirited debates, the founders of this country established a "compound republic of America," a system of "two distinct governments." THE FEDERALIST NO. 51 (James Madison). Under this system, the powers delegated to the federal government are "few and defined," THE FEDERALIST NO. 45 (James Madison). By contrast, those powers not expressly delegated to the federal government – which are reserved to the states, U.S. CONST. amend. X -- are "numerous and indefinite," and "extend to all the objects which, in the ordinary course of affairs, concern the lives, liberties, and properties of the people, and the internal order, improvement, and prosperity of the State." THE FEDERALIST NO. 45 (James Madison). The principles underlying the proper distribution and balance of power between these "two distinct governments" remain as viable today as when they were first articulated over two centuries ago.

In federal preemption cases, particularly those where Congress has "legislated . . . in a field which the States have traditionally occupied," the presumption is "that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress." *Medtronic, Inc. v. Lohr*, 518 U.S. 468, 485 (1996) (quoting *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218, 230 (1947); *Hillsborough County v. Automated Med. Labs., Inc.*, 471 U.S. 707, 715 (1985)).

Determining the "purpose of Congress is the ultimate touchstone in every pre-emption case." Mary J. Davis, *The "New" Presumption Against Preemption*, 61 HASTINGS L.J. 1217, 1220 (2010) (citing *Lohr*, 518 U.S. at 485); *Retail Clerks Int'l Ass'n, Local 1625 v. Schermerhorn*, 375 U.S. 96, 103 (1963)). Fundamental to preemption jurisdiction is the presumption against preemption, which dictates that courts should not presume "that a federal statute was intended to supersede the exercise of the power of the state unless there is a clear manifestation of intention to do so. The exercise of federal supremacy is not lightly to be presumed." *New York Dep't of Soc. Servs. v. Dublino*, 413 U.S. 405 (1973) (quoting *Schwartz v. Texas*, 344 U.S. 199, 202-03 (1952)). Issues concerning federalism are implicated the moment the Court "delve[s] into the murky realm of congressional purposes to ascertain whether Congress intended to displace state law." Robert S. Peck, *A Separation-of-Powers Defense of the "Presumption Against Preemption,"* 84 TUL. L. REV. 1185, 1199 (2010). Once this voyage into congressional intent has begun, it is fathomable that, given the opportunity, courts may overstep the carefully placed boundaries surrounding the spheres of dual sovereignty and preempt state tort law. This ill-advised voyage would improperly enable the federal government to intrude upon a field traditionally reserved for the States. *Id.*

The "presumption against preemption" is essential to the continued protection of state sovereignty and critical to the proper functioning of the procedural and political safeguards of federalism. States have historically maintained tort remedies against pharmaceutical manufacturers who fail to provide adequate warnings when that failure results in an injury. In fact, these state

tort remedies have coexisted with the federal regulation of the pharmaceutical industry for over seventy years. See David A. Kessler & David C. Vladeck, *Health Regulation and Governance: A Critical Examination of the FDA's Efforts to Preempt Failure-To-Warn Claims*, 96 GEO. L.J. 461, 462-63 (2008).

This case presents a claim implicating the health and safety of the citizens of two states, concerns historically within the province of the states. In this case, generic drug companies claim that failure to warn claims are preempted, even though the companies never even attempted to comply with their regulatory duty to ensure that the warnings on their label remained adequate; and even though the label of the drug at issue now contains a much stronger, boxed warning of exactly the adverse effect from which the plaintiffs suffer. Proper analysis thus requires the application of a presumption against preemption, not merely as a procedural nicety, but to fully respect both the historical balance of power between federal and state governments and the precedents of this Court.

Despite multiple amendments to the Food, Drug, and Cosmetic Act of 1962, 21 *U.S.C* § 301 et seq., Congress has not sought to preempt state tort litigation. Application of the presumption against preemption with the proper historical perspective will lead the Court to conclude—just as it recently held in *Wyeth v. Levine*, 129 *S.Ct.* 1187 (2009)—that federal law does not preempt failure to warn claims against generic drug companies. Instead, federal regulation and state tort law operate in this area as complementary pieces in an overall system of consumer protection. As such, this Court should affirm the lower courts' rulings, finding no federal preemption.

ARGUMENT

I. Federalism Necessarily Requires a "Presumption Against Preemption"

In its preemption analysis, this Court has "recognized the historic role of state law and paid homage to the role of states in our federal system of government." Davis, *The "New" Presumption Against Preemption*, 61 HASTINGS L.J. at 1218-19 (citing Caleb Nelson, *Preemption*, 86 VA. L. REV. 225 (2000)). This homage is explicitly stated when the Court references the fundamental principle—"presumption against preemption." *Id.* at 1219.

The long history of tort litigation in the pharmaceutical industry, particularly regarding the labeling of pharmaceutical drugs, coupled with the fact that Congress has not shown a clear and manifest intent to obliterate the state tort remedies to persons injured by pharmaceutical drugs, gives credence to the argument that this Court should not find federal preemption in this case. Mary J. Davis, *History of Regulation of the Pharmaceutical Industry*, 48 B.C. L. REV. 1089, 1140 (2007) (citing *Witczak v. Pfizer, Inc.*, 377 *F.Supp.* 2d 726, 728-29 (D. Minn. 2005); *Caraker v. Sandoz Pharm. Corp.*, 172 *F.Supp.* 2d 1018, 1031-39 (S.D. Ill. 2001)). Certainly, in the context of this matter, where the generic manufacturer shares the regulatory responsibility for including "a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved," 21 CFR § 201.57(e) (2005), the Court should not find that plaintiffs' claims arising out of their failure are barred by the manufacturer's attempt to shield themselves by brand maker's failure to comply

with this requirement. The ability of injured plaintiffs to bring tort claims directly speaks to the critical necessity of "the States' traditional ability to protect the health and safety of their citizens[.]" Davis, *History of Regulation*, 48 B.C. L. Rev. at 1095. Clearly, it is within the purview of the states to protect their citizens, who like Gladys Mensing and Julie Demahy, suffer from such a severe and irreversible neurological disorder as tardive dyskinesia, when a manufacturer knew that the incidence of injury for long-term users was so high. In fact, relying on *Cipollone v. Liggett Group, Inc.*, 505 *U.S.* 504 (1992), the Second Circuit Court of Appeals declared that "[t]he power of the states to govern this field is considerable and undisputed." *Cipollone*, 505 *U.S.* at 544 (Blackmun, J., concurring); *Desiano v. Warner-Lambert & Co.*, 467 *F.*3d 85, 86 (2d Cir. 2006).

Although the FDA regulatory process and state tort liability scheme "operate independently" of one another, "each provid[es] a significant, yet distinct, layer of consumer protection," Davis, *History of Regulation*, 48 B.C. L. Rev. at 1094 (citations omitted); Margaret Porter, *The Lohr Decision: FDA Perspective and Position*, 52 Food & Drug L.J. 7, 11 (1997), that is essential to the continued well-being of a functioning society. The States' tort liability scheme works in connection with the FDA's regulatory purpose. Generally speaking, tort liability serves interests that Congress did not fathom when it created the FDA. Tort liability compensates persons whose injuries occurred because of a pharmaceutical manufacturer's failure to provide adequate warnings. *See generally* Thomas O. McGarity, The Preemption War 33 (Yale 2008) (arguing "preemption completely eliminates that corrective justice role that common law courts have

played in this country since its founding"). However, tort law and its ability to seek accountability and preventive measures works towards the FDA's regulatory goals of protecting the health, safety, and general welfare of the people, even in instances where the federal agency fails in those regards. However, as the courts below point out, federal law provides no substitute for the remedy which state failure-to-warn claims have traditionally recognized. Thus, "in this case, the bar to a finding of preemption is set even higher. . . ." *Demahy v. Actavis, Inc.*, 593 *F.*3d 428, 435 (5th Cir. 2010). The States have the wherewithal and resources to compensate for the FDA's budgetary constraints and time limitations while providing a system where states are in a position to monitor risks that were unknown at the time of the FDA's approval. The States are also fully capable of acting quickly when an injury occurs or series of injuries occur. *See generally* McGarity, *supra* at 16 (calling Vioxx and the role that the FDA played in approving its safety for production "a profound regulatory failure").

Viewing the States as independent sovereigns within our federal republic—as the Framers did—it becomes readily apparent that the presumption that state laws—specifically, state tort remedies designed to compensate citizens for personal injuries—are well within the scope of the States' historic powers. These historic powers emanate directly from the Constitution and are further supported by the Federalist Papers. These "historic powers" may only be preempted when there is a clear and manifest purpose expressed by Congress. Yet, in this matter, petitioners concede that no express preemption exists, but instead argue "that it is impossible to comply with both federal and state law." *Demahy*, 593 *F.*3d at

434. However, requests to alter a labeling would not have violated federal or state law.

It stands to reason that tort liability is a field of law traditionally reserved for the States due to the localized impact of personal injury lawsuit on individual states. *See* Gary Schwartz, *Considering the Proper Federal Role in American Tort Law*, 38 ARIZ. L. REV. 917, 922 (1996); Samuel Issacharoff & Catherine M. Sharkey, *Backdoor Federalization*, 53 U.C.L.A. L. REV. 1353, 1384 (2006) (citations omitted). To find federal preemption in this case, this Court would be acting in direct contravention to the constitutional structure that Framers ultimately designed. The fundamental principles of federalism buttress this conclusion.

II. Historical Perspective of Federalism: State Sovereignty is the Rule and Federal Sovereignty is the Exception[2]

Federalism is critical to this Court's analysis of whether the federal law preempts state tort remedies. As did the Court in *Rice v. Santa Fe Elevator Corp.*, 331 *U.S.* 218 (1947), this Court's analysis here should begin with "the assumption that the historic police powers of the States [a]re not to be superseded by the [f]ederal [government] unless that was the clear and manifest purpose of Congress." *Rice*, 331 *U.S.* at 230 (citing *Napier v. Atlantic Coast Line R. Co.*, 272 *U.S.* 605, 611 (1926); *Allen-Bradley Local v. Wisconsin Employment Bd.*, 315 *U.S.* 740, 749 (1942)); *see generally Mintz v. Baldwin*, 289

2. *See* ALEXIS DE TOCQUEVILLE, DEMOCRACY IN AMERICA 115 (George Lawrence trans., J.P. Mayer ed., Harper Perennial 1966).

U.S. 346, 350-52 (1933) (recognizing the "presumption against preemption"). The *Rice* Court set forth a principle of significant constitutional dimension, recognizing the necessity of protecting state sovereignty while ensuring that the structural, procedural, and political safeguards[3] of federalism remain firmly in place, just as the Framers intended. *Rice*, 331 *U.S.* at 230.

In 1869, this Court addressed "the constitutional scheme of dual sovereigns:

> [T]he people of each State compose a State, having its own government, and endowed with all the functions essential to separate and independent existence, . . . [W]ithout the States in union, there could be no such political body as the United States. Not only, therefore, can there be no loss of separate and independent autonomy to the States, through their union under the Constitution, but it may be not unreasonably said that the preservation of the States, ad the maintenance of their governments, are as much within the design and care of the Constitution as the preservation

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3. "Federal lawmaking was thus consciously held hostage to the 'political safeguards of federalism,' to borrow Herbert Wechsler's famous phrase." Henry Paul Monaghan, *Supremacy Clause Textualism*, 110 COLUM. L. REV. 731 (2010) (quoting Bradford R. Clark, *Federal Lawmaking and the Role of Structure in Constitutional Interpretation*, 96 CAL. L. REV. 699, 701 (2008) (quoting Herbert Wechsler, *The Political Safeguards of Federalism: The Role of the States in the Composition and Selection of the National Government*, 54 COLUM. L. REV. 543, 543 (1954)).

> of the Union and the maintenance of the National government. The Constitution, in all its provisions, looks to an indestructible Union, composed of indestructible States.
>
> [*Gregory v. Ashcroft*, 501 *U.S.* 452, 457 (1991) (quoting *Texas v. White*, 7 *Wall.* 700, 725 (1869) (in turn, quoting *Lane County v. Oregon*, 7 *Wall.* 71, 76 (1869)) (internal quotation marks omitted)].

The *Gregory* Court recognized this fundamental principle—dual sovereignty—as arising from the axiom that, "under our federal system, the States possess sovereignty concurrent with that of the Federal Government, subject only to limitations imposed by the Supremacy Clause." *Gregory*, 501 *U.S.* at 457 (quoting *Tafflin v. Levitt*, 493 *U.S.* 455, 458 (1990)); *see generally* ALEXIS DE TOCQUEVILLE, DEMOCRACY IN AMERICA 58 (George Lawrence trans., J.P. Mayer ed., Harper Perennial 1966) ("If there is one country in the world where one can hope to appreciate the true value of the dogma of the sovereignty of the people, study its application to the business of society, and judge both its dangers and its advantages, that country is America.").

After much debate, the Framers resolved to specifically create a federal government "of limited powers." *Gregory*, 501 *U.S.* at 457. The people have never altered that principle. Congress has never altered that principle. No Constitutional Amendment has altered that principle. As a matter of fact, the Tenth Amendment to the Constitution provides that "[t]he powers not delegated to the United States by the constitution, nor prohibited by

it to the states, are reserved to the states, respectively, or to the people." U.S. CONST. amend. X. In the Federalist Papers, James Madison succinctly stated that "[t]he powers delegated by the proposed Constitution to the federal government, are few and defined." THE FEDERALIST No. 45 (James Madison). Madison expounding the virtue of a limited federal government, declaring that (1) the powers of the States were to be "numerous and indefinite" and (2) these powers were to "extend to all the objects which, in the ordinary course of affairs, concern the lives, liberties, and properties of the people, and the internal order, improvement, and prosperity of the State." THE FEDERALIST No. 45 (James Madison). Whereas the powers of the federal government were to be principally exercised on "external objects, as war, peace, negotiation, and foreign commerce; with which last the power of taxation will, for the most part, be connected." THE FEDERALIST No. 45 (James Madison); *see generally* ALEXIS DE TOCQUEVILLE, DEMOCRACY IN AMERICA 114-17 (George Lawrence trans., J.P. Mayer ed., Harper Perennial 1966) (1835) (explaining that "the attributes of the federal government were carefully defined, and it was declared that everything not contained within that definition returned to the jurisdiction of state governments.").

"The federalization of tort law finds no support in the annals of early American history." John C. Toro, *Why Principles of Federalism and Communitarianism Demand That Tort Law be Left up to the States*, 7 GEO. J.L. PUB. POL'Y 655, 658 (2009). As the Framers intended, the field of tort law traditionally has been, almost exclusively, reserved to the States. *Id.* at 658 (quoting Robert M. Ackerman, *Tort Law and Federalism: Whatever Happened to Devolution?*, 14 YALE L. & POL'Y

REV. 429, 430 (1996)). In careful precision, the Framers created a republic where the States would govern the majority of fields, including tort litigation. The purpose was to ensure the active participation of the people at a local level. *Id.* at 658; *see generally* THE FEDERALIST No. 45 (James Madison).

This federalist structure envisioned by the Framers was deliberately designed to preserve numerous advantages given to the people, but also to "ensure the protection of 'our fundamental liberties.' " *Atascadero State Hosp. v. Scanlon*, 473 *U.S.* 234, 242 (1985) (citing *Garcia v. San Antonio Metro. Transit Auth.*, 469 *U.S.* 528, 572 (1985) (Powell, J., dissenting) (internal quotation marks omitted); *see also Wyeth v. Levine*, 129 *S.Ct.* 1187, 1205 (2009)(Thomas, J., concurring) (expounding the notion that a "'federalist structure of joint sovereigns preserves to the people numerous advantages,' such as 'a decentralized government that will be more sensitive to the diverse needs of a heterogeneous society' and 'increase[d] opportunity for citizen involvement in democratic processes[.]' "). This "constitutionally mandated balance of power," *Atascadero*, 473 *U.S.* at 242, was designed to "reduce the risk of tyranny and abuse" from the States or the federal government. *Gregory*, 501 *U.S.* at 458; *see* Erwin Chemerinsky, *Empowering States When It Matters: A Different Approach to Preemption*, 69 BROOK. L. REV. 1313, 1325 (2004) (explaining that "[t[his constitutionally mandated division of authority was adopted by the Framers to ensure protection of our fundamental liberties" (internal quotation marks and citation omitted)).

Alexander Hamilton, in the Federalist Papers, stated that the envisioned federalist structure would be

> more competent to a struggle with the attempts of the government to establish a tyranny. But in a confederacy the people, without exaggeration, may be said to be entirely the master of their own fate. Power being almost always the rival of power, the general government will at all times stand ready to check the usurpations of the state governments, and these will have the same disposition towards the general government. The people, by throwing themselves into either scale, will infallibly make it preponderate. If their rights are invaded by either, they can make use of the other as the instrument of redress.
>
> [THE FEDERALIST No. 28 (Alexander Hamilton)].

Similarly, in The Federalist Papers, James Madison addressed the same issue. Stating that "[t]here are [] two considerations particularly applicable to the federal system of America, which place that system in a very interesting point of view[,]" Madison declared that

> *First.* In a single republic, all the power surrendered by the people is submitted to the administration of a single government; and the usurpations are guarded against by a division of the government into distinct and separate departments. In the compound republic of America, the power surrendered by the people is first divided between two

> distinct governments, and then the portion allotted to each subdivided among distinct and separate departments. Hence a *double security* arises to the rights of the people. The different governments will control each other, at the same time that each will be controlled by itself.
>
> *Second.* It is of great importance in a republic not only to guard the society against the oppression of its rulers, but to guard one part of the society against the injustice of the other part. Different interests necessarily exist in different classes of citizens. If a majority be united by a common interest, the rights of the minority will be insecure. . . .
>
> [THE FEDERALIST No. 51 (James Madison)].

In order for Madison's "double security" to be effective, the balance of power between the States and the federal government must be properly maintained. *Gregory*, 501 *U.S.* at 459. "These twin powers will act as mutual restraints only if both are credible. [Within] the tension between federal and state power lies the promise of liberty." *Id.* at 459. Nevertheless, as this Court articulated, "[t]he Federal Government holds a decided advantage in this delicate balance: the Supremacy Clause." *Gregory*, 501 *U.S.* at 460; *see also* U.S. CONST. art. VI, cl. 2. Recognizing that Congress "may impose its will on the States" and "may legislate in areas traditionally regulated by the States," this Court has stated that this "extraordinary power" is one that "we must assume Congress does not exercise lightly." *Gregory*, 501 *U.S.* at 460; *see generally Wyeth*, 129 *S.Ct.* at 1205.

Recognizing the import of the structural, procedural, and political safeguards of federalism, Justice Brandeis once declared:

> To stay experimentation in things social and economic is a grave responsibility. Denial of the right to experiment might be fraught with serious consequences to the Nation. It is one of the happy incidents of the federal system that a single courageous State may, if its citizens choose, serve as a laboratory; and try novel social and economic experiments without risk to the rest of the country.
>
> [Samuel Issacharoff & Catherine M. Sharkey, *Backdoor Federalization*, 53 U.C.L.A. L. REV. 1353, 1355 (2006) (quoting *New State Ice Co. v. Liebemann*, 285 *U.S.* 262, 311 (1932) (Brandeis, J., dissenting)].

The deliberate design of dual sovereigns described above necessarily leads to two conclusions: (1) that the "States retain a substantial sovereign authority," *Wyeth*, 129 *S.Ct.* at 1205-06 (citations omitted); *see Tafflin*, 493 *U.S.* at 458, and (2) that the "tacit postulates" of the Constitution described by Chief Justice Burger and Justice Rehnquist are "as much engrained in the fabric of the documents as its express provisions." *Nevada v. Hall*, 440 *U.S.* 410, 433 (1979) (Rehnquist, J., dissenting) (noting that without the "tacit postulates . . . the Constitution is denied force and often meaning"); *see generally* LAURENCE H. TRIBE, CONSTITUTIONAL CHOICES 50 (1985).

III. Constitutional Perspective: the Supremacy Clause, Preemption, and Separation of Powers

Succinctly stated, the Supremacy Clause is "the provision at the epicenter of the constitutional structure" envisioned by the Framers. Henry Paul Monaghan, *Supremacy Clause Textualism*, 110 COLUM. L. REV. 731 (2010) (quoting Bradford R. Clark, *Federal Lawmaking and the Role of Structure in Constitutional Interpretation*, 96 CAL. L. REV. 699, 724 (2008)). Of particular note, during the debates at the Constitutional Convention, the Framers contemplated, but ultimately rejected, a "stronger version of the Supremacy Clause under which the National Legislature would have been [e]mpowered . . . to negative all laws passed by the several States, contravening in the opinion of the National Legislature the article of Union." Alan Untereiner, *The Defense of Preemption: A View From the Trenches*, 84 TUL. L. REV. 1257, 1258 (2010) (internal quotation marks and citation omitted) (citing James Madison, Notes on the Constitutional Convention (May 29, 1787), in 1 The Records of the Federal Convention of 1787, at 21 (Max Farrand ed., 1911).

As it exists today, the Supremacy Clause "must operate only in accordance with its terms," if the task of maintaining the "delicate balance of power mandated by the Constitution" is to be achieved. *Wyeth*, 129 *S.Ct.* at 1206 (Thomas, J., concurring). The language of the clause provides:

> This constitution, and the laws of the United States which shall be made in pursuance thereof, and all treaties made, or which shall be made, under the authority of the United States,

> shall be the supreme law of the land; and the judges in every state shall be bound thereby, anything in the constitution or laws of any sate to the contrary nothwithstanding.
>
> [U.S. Const. art. VI, cl. 2.]

Entrenched within the Supremacy Clause is the basic presumption that state laws are *not* to be preempted. This Court has explained that this presumption arises from the recognition that " 'States are independent sovereigns in our federal system, [and courts] have long presumed that Congress does not cavalierly [preempt] state-law causes of actions.' " Peck, *"Presumption Against Preemption,"* 84 Tul. L. Rev. at 1195 (citing *Medtronic, Inc. v. Lohr*, 518 *U.S.* 470, 485 (1996); *see generally Cal. Fed. Sav. & Loan Ass'n v. Guerra*, 479 *U.S.* 272, 281 (1987). This fundamental presumption is often justified by maxims of federalism. *See generally Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 *U.S.* 141, 166-67 (1989); *Tafflin*, 493 *U.S.* at 458. As Professor Caleb Nelson adeptly explains, the Framers created the preemption mechanism for where there is an actual conflict, not a speculative or potential conflict. Nelson, *Preemption*, 86 Va. L. Rev. at 259-61. "Under the Supremacy Clause, then, the test for preemption is simple: Courts are required to disregard state law if, but only if, it contradicts a rule validly established by federal law." *Id.*

As illustrated by this Court's preemption jurisprudence, *see Wyeth v. Levine*, 129 *S.Ct.* 1187 (2009), the implementation of preemption depends upon congressional intent; therefore, because of this reliance, "a freewheeling inquiry that ends up supplying [the] *missing* legislative intent implicates separation of powers." Peck,

"Presumption Against Preemption," 84 TUL. L. REV. at 1197; *see also Wyeth*, 129 *S.Ct.* at 1217 (Thomas, J., concurring) (explaining that "freewheeling, extratextual, and broad evaluations of the purposes and objectives embodied within federal law . . . lead[] to decisions giving improperly broad pre-emptive effect to judicially manufactured policies, rather than to the statutory text enacted by Congress."

The concept of separation of powers is of transcendent importance to our federal republic. In debating the framework for our republic, Thomas Jefferson declared that separation of powers was "the first principle of a good government." Peck, *"Presumption Against Preemption,"* 84 TUL. L. REV. at 1196 (citing GORDON S. WOOD, THE CREATION OF THE AMERICAN REPUBLIC 1776-87 604 (1969); GERHARD CASPER, SEPARATING POWER: ESSAYS ON THE FOUNDING PERIOD 1 (1997)("[S]eparation of governmental power along functional lines has been a core concept of American constitutionalism. . . ."). The structural dynamic of separation of powers not only "reflects the 'central judgment of the Framers of the Constitution that, within our political scheme, the separation of governmental powers into three" distinct branches, *Mistretta v. United States*, 488 *U.S.* 361, 380 (1989); but it is "essential to the preservation of liberty." Peck, *"Presumption Against Preemption,"* 84 TUL. L. REV. at 1196.

As James Madison intended, the complicated and intricate design of our federal republic diffuses the "power surrendered by the people . . . among distinct branches, as well as between the federal and the local, to guard against despotism." *Id.* at 1196 (citing HENRY STEELE COMMAGER, THE EMPIRE OF REASON: HOW EUROPE IMAGINED AND AMERICA REALIZED THE ENLIGHTENMENT 194 (1977)).

The presumption against federal preemption "comports with the fundamental principles of federalism articulated by the Supreme Court: By declining to infer preemption in the face of congressional ambiguity, the Court is not interposing a judicial barrier to Congress's will in order to protect state sovereignty . . . but is instead furthering the spirit of [its federalism decisions] by requiring that decisions restricting state sovereignty be made in a deliberate manner by Congress, through the explicit exercise of its lawmaking power to that end." Peck, *"Presumption Against Preemption,"* 84 TUL. L. REV. at 1195 (citing LAURENCE H. TRIBE, AMERICAN CONSTITUTIONAL LAW 480 (2d ed. 1988).

It is not an unreasonably extreme notion that the "courts would violate the principle of federalism by abrogating a state's power to protect its citizens' health and safety absent a clear congressional expression to abrogate that power." *Id.* at 1196 (citing Richard C. Ausness, *Federal Preemption of State Products Liability Doctrines*, 44 S.C. L. REV. 187, 248 (1993)). Furthermore, without a congressional expression of clear and manifest intent, the utilization of federal preemption forces the Court to step into the role of the Legislative branch; and, thus overstep the bounds that exist between the two spheres of legislative and judicial powers. *Ibid.*

CONCLUSION

For the foregoing reasons, *amicus curiae* the American Association for Justice urges this Court to affirm the judgments of the Eighth Circuit Court of Appeals and the Fifth Circuit Court of Appeals.

Respectfully submitted,

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AMICUS CURIAE BRIEF

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In the Supreme Court of the United States

PLIVA, Inc., et al., 09-993 *vide* 09-1039, *Petitioners*,

v.

Gladys Mensing, *Respondent*.

Actavis Elizabeth, LLC, 09-1039 *vide* 09-993, *Petitioner*,

v.

Gladys Mensing, *Respondent*.

Actavis, Inc., 09-1501, *Petitioner*,

v.

Julie Demahy, *Respondent*

On Writs of Certiorari to the United States Courts of Appeals for the Fifth and Eighth Circuits

BRIEF OF THE AMERICAN MEDICAL ASSOCIATION, TEXAS MEDICAL ASSOCIATION, TEXAS MEDICAL LIABILITY TRUST, TEXAS ALLIANCE FOR PATIENT ACCESS, NORTH CAROLINA MEDICAL SOCIETY, CALIFORNIA MEDICAL ASSOCIATION, LOUISIANA MEDICAL MUTUAL INSURANCE COMPANY, AND LOUISIANA STATE MEDICAL SOCIETY AS *AMICI CURIAE* IN SUPPORT OF RESPONDENTS

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INTEREST OF AMICI CURIAE[1]

The American Medical Association ("AMA") is the largest professional association of physicians, residents and medical students in the United States. Additionally, through state and specialty medical societies and other physician groups seated in its House of Delegates, substantially all United States physicians, residents and medical students are represented in the AMA's policy making process. The objectives of the AMA are to promote the science and art of medicine and the betterment of public health.

The AMA joins this brief on its own behalf and as a representative of the Litigation Center of the American Medical Association and the State Medical Societies. The Litigation Center is a coalition among the AMA and the medical societies of each state, plus the District of Columbia, whose purpose is to represent the viewpoint of organized medicine in the courts.

The Texas Medical Association ("TMA") is a medical professional membership association (an IRC section 501c6 Texas non-profit corporation) of over 45,000 physicians licensed by the State of Texas, medical residents and medical students. The interests that the Texas Medical Association seeks to protect through this lawsuit are germane to its organizational purpose. One mission of TMA—in fact, its primary mission—is to improve the health of all Texans by

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[1] Pursuant to Rule 37.6, Amici Curiae state that no counsel for a party authored this brief in whole or in part, and that no party or counsel for a party, other than Amici Curiae made a monetary contribution intended to fund this brief's preparation or submission. Each party has consented to the filing of this brief.

being an advocate for patients and the profession of medicine. By filing this brief, TMA is seeking to limit the adverse consequences for patients and physician defendants in medical professional liability litigation when the primary defendant is in fact the drug manufacturer.

The Texas Medical Liability Trust ("TMLT") is a not-for-profit health-care liability claim trust owned by its physician policyholders. TMLT was created in 1979, as a result of a legislatively-recognized health-care and medical malpractice crisis, to provide an affordable and stable source of professional liability insurance to Texas physicians. TMLT is an independent insurer writing professional liability policies for more than 14,000 Texas physicians and health-care providers. TMLT is extensively involved in underwriting and risk management matters for the health-care industry, and this requires TMLT to maintain knowledge and expertise of insurance industry standards as well as jurisprudential standards that affect liability insurance procurement and costs in Texas. TMLT is vitally interested in the consistency and predictability of Texas state, as well as federal courts' decision making in cases involving professional liability of physicians and health-care providers.

The Texas Alliance for Patient Access ("TAPA") is an association of over 250 health-care interests providing medical care to Texas residents. Its members include physicians, nurses, therapists, hospitals, trade associations, malpractice insurance carriers, managed care providers, and other individuals and entities that have an interest in assuring timely and affordable access to quality

medical and health care. TAPA seeks to improve access to health care by passing meaningful and sustainable medical liability reforms, requiring that TAPA maintain knowledge and expertise of jurisprudence standards affecting health care liability and liability insurance procurement and costs in the State of Texas.

The North Carolina Medical Society (the "Medical Society") is the largest physician organization in North Carolina. Originally founded in 1849, more than 150 years later, the Medical Society has approximately 11,000 members. The Medical Society unifies doctors across North Carolina in all specialties and work settings on issues related to, *inter alia*: the physician-patient relationship, health regulation, and patient safety. As the largest physician organization in North Carolina, the Medical Society devotes significant resources to advocating physician viewpoints in the public policy arena. Specifically, the Medical Society and its member physicians take an active role in issues addressed by private companies, institutions, and the state government and work to ensure that the views of the medical community are presented in an organized and effective fashion.

The California Medical Association ("CMA") is a nonprofit, incorporated professional association of more than 35,000 physicians who are engaged in the private practice of medicine, in all specialties and modes of practice, in the State of California. Its mission is to promote the science and art of medicine, the care and well-being of patients, the protection of the public health, and the betterment of the medical profession.

CMA and the thousands of physicians and patients it represents have their highest priority insuring that patients receive the best medical care possible. For that reason, CMA and its members diligently monitor and carefully consider the consequences to patients of important public policy issues such as preemption of pharmaceutical failure-to-warn claims. To protect patient safety, CMA files this brief in support of Respondents Gladys Mensing and Julie Demahy on its own behalf and on behalf of its members' patients who will be directly and adversely affected by preemption.

Louisiana Medical Mutual Insurance Company ("LAMMICO") is the largest medical professional liability insurer in Louisiana. LAMMICO was formed as a mutual company by physicians in 1981 to develop and deliver insurance products and services at the lowest rates consistent with sound operating principles. LAMMICO currently insures 6,000 physicians and other health-care providers, most of whom are located in Louisiana. LAMMICO is an advocate for the health-care community and patients. As such, LAMMICO has a substantial and legitimate interest that will be affected by this case.

The Louisiana State Medical Society ("LSMS") was founded in 1878 by a group of 80 physicians representing 14 parishes. Today, the society is a professional association of approximately 5,200 physicians who practice medicine in Louisiana and 1,350 medical student members. LSMS is a voluntary association of physicians providing leadership for the advancement of the health of Louisiana residents and serving as the premier advocate for patients and physicians. The members of the society practice in all fields of medicine.

SUMMARY OF THE ARGUMENT

The hallmark decision in *Wyeth v. Levine*[2] declared that brand name drug manufacturers bear ultimate responsibility for the content of their pharmaceutical product labels at all times and that Congress did not intend to preempt this duty in the Food, Drug and Cosmetic Act ("FDCA"). This Honorable Court is now presented with the opportunity to extend this policy to generic drug manufacturers as well. The arguments and considerations that compelled the result in *Levine* likewise urge a holding that generic drug makers have a duty to perform affirmative post-marketing safety surveillance and to act upon information gained in this process. The Medical Associations[3] respectfully propose that it should be the manifest public policy of this nation that all drug manufacturers – brand and generic – have a continuing duty to conduct themselves as vigilant, active, and responsible members of the health-care community in furtherance of the safety and well being of the American public.

The foremost priority of all physicians is the health of their patients. Prescription drugs serve as a critical ally in the treatment and cure of illness and disease. Even so, physicians must perform a risk-benefit analysis each time they prescribe a drug; this process requires knowledge of current and accurate drug safety information. Physicians have neither the manpower, nor the training or ability to conduct

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[2] 129 S. Ct. 1187 (2009).

[3] As used herein, "The Medical Associations" includes Amici Curiae, AMA, TMA, the Medical Society, CMA, and LSMS.

expansive post-marketing safety surveillance of drugs they utilize.

Physicians attempt to stay abreast of critical developments regarding the safety of drugs, with the drug maker serving as an essential source of product information. Physicians and other health-care providers rely upon the pharmaceutical industry to provide them with safe and effective medicines, subject to oversight of the Food and Drug Administration ("FDA"); this includes accurate and current information regarding the benefits and risks of pharmaceutical products.

It would disrupt the established patient care system to adopt a policy pursuant to which one member of the health-care community – generic drug manufacturers – was permitted to absolve themselves of their unique and vital role in ongoing drug safety. The policy of the medical community should be to enhance every reasonable mechanism that results in a better informed patient and physician population and, thereby, afford greater patient safety.

ARGUMENT

A. Comprehensive and Active System of Post-Marketing Safety Surveillance is of Vital Importance to Patient Health and Safety

The concept that drug safety is of paramount importance has long been held sacrosanct by the medical and scientific community. It is for this reason that The Medical Associations advocate a comprehensive and ongoing system by which drug

safety may be actively monitored.[4] This is not a passive endeavor; all participants in the manufacture and marketing of pharmaceutical products have a continuing duty to conduct themselves as vigilant, responsible members of this health-care team.

Levine implicitly recognizes a redundant and dynamic pharmacovigilance network is an important element of post-marketing drug safety. At the foundation of this network, however, is the declaration set forth in *Levine*: manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times.[5]

History proves that the current drug approval system "virtually guarantees that the full risks and complete safety profile of [prescription] drugs will not be identified at the time of approval."[6] "FDA product approval and state tort liability usually operate independently, each providing a significant, yet distinct, layer of consumer protection."[7] Although it

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[4] *Code of Ethics Opinion 9.032 -- Reporting Adverse Drug or Device Events*, AM. MED. ASS'N (1994), http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics/opinion9032.shtml (last visited Feb. 16, 2011); *AMA Policy H-125.984*, AM. MED. ASS'N (June 2007), http://www.ama-assn.org/ama/no-index/about-ama/17731.shtml.

[5] 129 S. Ct. at 1197-98.

[6] DeAngelis, C., *et al.*, *Prescription Drugs, Products Liability, and Preemption of Tort Litigation*, 300 (16) J. AM. MED. ASS'N, 1939-41 (2008).

[7] Porter, M, *The Lohr Decision: FDA Perspective and Position*, 52 FOOD DRUG L. J. 7, 11 (1997).

would be preferable to not be dependent on our justice system as a safety mechanism, experience proves that the elimination of a duty to reasonably conduct active safety surveillance will "result in the reduced safety of drugs ... for the American people."[8] The medical community holds firm to the belief that all reasonable and prudent steps should be employed to assure the sustained viability and safety of prescription drugs.

The guiding principles of *Wyeth v. Levine*[9] inform the disposition of the issues here. There, the Court remarked that Congress has historically sought to ensure that the FDA "protect the public health" and "assure the safety, effectiveness, and reliability of drugs."[10] Since 1906, Congress has established a legislative framework intended to "bolster consumer protection against harmful products."[11] It is well recognized that the "FDA has limited resources to monitor the 11,000 drugs on the market," particularly "in the post-marketing phase as new risks emerge."[12] The evolution of the FDA's role and legislative mandate, along with an understanding about the convergence of medicine and law, supports the conclusion that "Congress did not intend FDA oversight to be the exclusive means of ensuring drug

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[8] Curfman, G., *et al.*, *Why Doctors Should Worry About Preemption*, 359(1) N. ENG. J. MED. 1, 1 (July 3, 2008).

[9] 129 S. Ct. 1187 (2009).

[10] *Id.* at 1197.

[11] *Id.* at 1199.

[12] *Id.* at 1202.

safety and effectiveness."[13] On the contrary, both the statutory framework and case law support the notion of an affirmative duty owed by drug manufacturers – regardless of their position in line – to maintain the accuracy and adequacy of labels for products they sell.[14]

The *Mensing* and *Demahy* appeals "are premised on a more fundamental misunderstanding"[15] regarding drug safety and responsibility. Regardless of their character as a brand or generic manufacturer, it should be inherently obvious that the manufacturer of a prescription drug "bears responsibility for the content of its label at all times. It is charged both with crafting an adequate label and with insuring that its warnings remain adequate as long as the drug is on the market."[16] To hold otherwise would do violence to the spirit and eviscerate the purpose of the FDA regulatory scheme, and would amount to "an untenable interpretation of congressional intent."[17]

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[13] *Id.* at 1200.

[14] *See generally* Ramey, M., *Conte v. Wyeth: Caveat Innovator and the Case for Perpetual Liability in Drug Labeling*, 4 PITT. J. ENVTL. & PUB. HEALTH L. 73 (2010), http://pjephl.law.pitt.edu/files/Ramey.pdf.

[15] *Levine*, 129 S. Ct. at 1201.

[16] *Id.*

[17] *Id.*

B. Assuring Product Safety Mandates An Ongoing Duty to Monitor and Take Action

The Medical Associations advocate a national public policy declaring that all pharmaceutical manufacturers must actively and diligently participate in the surveillance of product quality; hence, there is an ongoing duty to monitor and to act.[18] The burden to exercise prudence in drug safety is one borne by drug manufacturers and supported by health-care professionals.[19] When safety concerns are discovered, the drug maker must act in a timely manner to warn customers, utilizing labeling revisions, communications to health-care providers, or alternative means consistent with the conduct of a responsible product manufacturer. The goal is to effectively communicate current product safety information in any means allowed by law using every resource at the disposal of the industry and the FDA.

Petitioners seek to shift the weight of this important responsibility for product safety to the other parties in the health-care delivery system. Petitioners

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[18] *Code of Ethics Opinion 9.032 -- Reporting Adverse Drug or Device Events*, *supra* note 4; *AMA Policy H-125.984*, *supra* note 4.

[19] The American Medical Association supports a strong FDA (*e.g.*, Health and Ethics Policy H-100.980) and enhanced physician access to drug adverse event data (*e.g.*, House of Delegates Directive D-100.982). AMA ethical policy recognizes that "[s]pontaneous reports of adverse events are irreplaceable as a source of valuable information about drugs and medical devices, particularly their rare or delayed effects, as well as their safety in vulnerable patient populations." *Code of Ethics Opinion 9.032 -- Reporting Adverse Drug or Device Events*, *supra* note 4; *see also AMA Policy H-125.984*, *supra* note 4.

first assert that this duty is shared between the FDA and the brand manufacturer.[20] This broad policy argument was rejected in *Levine*.

Second, generic drug defendants typically employ a litigation strategy that implicates the prescribing physician. The first prong of this defense is that the prescriber did not rely on the label for the specific generic drug at issue; this argument ignores the fact that the brand and generic labels are identical. Alternatively, the generic manufacturer contends that the physician was a "learned intermediary" to whom the duty to inform was solely owed.[21] Under either scenario, the generic drug maker seeks to escape any legal repercussions. Concern about the lack of a legal remedy for the injured patient would be "misplaced," because the patient could assert "state law claims against their physicians" who, it is commonly alleged, used the drug product in a manner inconsistent with the product labeling.[22] Amici Curiae conclude, therefore, that the position proposed by Petitioners is that the FDA, brand manufacturers, and prescribing physicians have an ongoing responsibility for product safety and warnings, while the actual, generic drug

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[20] Petitioner Pliva's Reply Brief at 1: Congress and the FDA placed "the burden of prescription drug labeling content on the branded drug manufacturer and the FDA...." *See also* Brief of Petitioner Actavis at 20.

[21] *See, e.g.*, *Pustejovsky v. PLIVA, Inc.*, 623 F.3d 271, 274 (5th Cir. 2010). The incongruity of these defense arguments is apparent; but, this strategy is pursued nonetheless.

[22] Brief of Petitioner Actavis, Inc. at 26, n. 14.

manufacturer has a limited obligation. This conclusion is neither equitable nor realistic.[23]

The scientific basis offered for excusing generic drug makers from a duty to affirmatively monitor and safeguard their products is that, "by the time a branded drug is eligible to generic versions, the safety profile of the drug has been identified; i.e., those adverse events that did not surface during the pre-approval clinical studies generally are identified."[24] Unfortunately, this assertion is not supported by historical fact.

The archives of medical- and product-liability litigation are replete with examples of drugs marketed for many years, yet their safety profiles remain elusive. The "fen-phen" litigation centered on the drug fenfluramine (Pondimin), introduced to the United States market in 1973. This drug, in combination with phentermine, became widely popular as a weight-loss therapy in the 1990s. In 1996[25] and 1997,[26] two

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[23] Even proponents of preemption for brand name drug manufacturers concede that the generic preemption argument is not commercially plausible ("we don't want our clients left holding the liability bag when they didn't sell the product and thus didn't make any profit from it"). *See Government Opposes Certiorari In Mensing Generic Preemption Case*, DRUG AND DEVICE L. (Nov. 4, 2010), http://druganddevicelaw.blogspot.com/search/label/Generic%20Drugs.

[24] Supplemental Brief of Petitioner Pliva at 13; *see also* Amicus Brief of Generic Pharmaceutical Association, at 17.

[25] Abenhaim, L., *et al.*, *International Primary Pulmonary Hypertension Study (IPPHS), Appetite-Suppressant Drugs and the*

scientific articles brought to light significant pulmonary and cardiac adverse events that were not known or appreciated during the twenty-plus-year history of marketing of these drugs. Pondimin was withdrawn from the market in late 1997, leaving a legacy of a latent injury undiscovered by way of customary safety surveillance processes.

Propoxyphene is an opioid medication first approved by the FDA in 1957. This drug was sold in both brand and generic forms. In November 2010, based on newly-accumulated safety data, the FDA determined "the post-marketing safety signals for this drug dictated that the overall balance of risk and benefit can no longer be considered favorable." The agency thus recommended that propoxyphene products be removed from the United States market.[27]

Non-steroidal anti-inflammatory drugs ("NSAIDs") have been on the market since the 1970s. Examples include Motrin (ibuprofen) and Naprosyn (naproxen). The product labels for NSAIDs have been modified on an ongoing basis as the science pertaining to these drugs evolves. The most prominent changes include

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Risk of Primary Pulmonary Hypertension, 335(9) N. ENG. J. MED. 609 (Aug. 29, 1996).

[26] Connolly, H., *et al.*, *Valvular Heart Disease Associated With Fenfluramine-Phentermine*, 337(9) N. ENG. J. MED. 581, 588 (Aug. 28, 1997).

[27] *Propoxyphene-Containing Products*, U.S. FOOD AND DRUG ADMIN. (Dec. 6, 2010), http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm233800.html.

the addition of a black box warning and the implementation of a Medication Guide "highlighting the potential for increased risk of cardiovascular (CV) events and the well described, serious, potential life-threatening gastrointestinal (GI) bleeding associated with their use."[28] Labeling changes such as these are an important source of product safety information and result in different prescribing practices and patient perceptions. NSAID products are still on the United States market and are frequently prescribed, thereby rendering ongoing research and study a valid endeavor.

A timely example of the necessity of vigorous and continuous post-marketing safety surveillance is offered by the drug terbutaline sulfate. This drug was originally approved in the 1970s and was indicated for treatment of asthma. The drug has since evolved as a treatment for preterm labor in obstetrical patients. On February 17, 2011, the FDA announced that it was requiring a black box warning on this drug. "The decision to require a Boxed Warning and Contraindication is based on the FDA's review of post-market safety reports of heart problems and even death associated with terbutaline use for obstetric indications, as well as data from medical literature documenting the lack of safety and effectiveness of

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[28] *COX-2 Selective (includes Bextra, Celebrex, and Vioxx) and Non-Selective Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)*, U.S. FOOD AND DRUG ADMIN. (Apr. 7, 2005), http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm103420.htm. This link contains a listing of all non-steroidal anti-inflammatory drugs. NSAIDs are marketed as prescription and generic, as well as over-the-counter products.

terbutaline for preventing preterm labor, and animal data suggesting potential risks."[29] The safety announcement is particularly relevant to the discussion at hand because, as the FDA noted, "[t]here are multiple generic versions of terbutaline oral tablets and injectable formulations available. The brand name products were previously discontinued by the companies that made them."[30] Terbutaline, therefore, is a stark example of a drug that has no surveillance oversight by "the brand." Continuous, aggressive, and ongoing pharmacovigilance by the generic drug manufacturers is an absolute necessity to ensure patient safety. It is foreseeable that this scenario will be repeated many times as the pharmaceutical landscape evolves in the United States.

Metoclopramide is a final example of an old drug for which recent drug safety data prompted new label warnings. Reglan, the innovator drug, was approved by the FDA in 1980. The drug is now sold primarily in generic form. The product label historically included a warning about tardive dyskinesia; however, concerns about the adequacy of the label and the fact that the drug was routinely used for the long term resulted in the allegation that the label was misleading as to the risk level for developing this condition.[31] In 2009, the

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[29] *FDA News Release: FDA Warns Against Certain Uses Of Asthma Drug Terbutaline For Preterm Labor: Certain Uses Could Lead To Maternal Heart Problems And Death*, U.S. FOOD AND DRUG ADMIN. (Feb. 17, 2011), http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm243840.htm.

[30] *Id.*

[31] *See, e.g.*, *McNeil v. Wyeth*, 462 F.3d 364, 373 (5th Cir. 2006).

FDA concluded that "new safety information"[32] required the implementation of a Risk Evaluation and Mitigation Strategy ("REMS") and labeling modifications, including the addition of a black box warning. Now, when a patient obtains a prescription for metoclopramide, it is required by law[33] that the patient be provided with the patient Medication Guide.[34] The use of a Medication Guide is a clear means of placing responsibility for communicating product safety information on the drug manufacturer. The policy of implementing REMs and the use of Medication Guides is persuasive evidence of congressional intent that the drug manufacturer has a continuing, active, and potentially direct responsibility to consumers to warn them of the risks of prescription drugs.[35]

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[32] "This information was not available when your ANDA was approved. We consider this information to be 'new safety information' as defined in FDAAA." U.S. FOOD AND DRUG ADMIN., http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM111378.pdf (last visited Feb. 25, 2011).

[33] "Under 21 C.F.R. 208 and in accordance with 505-1, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Reglan (metoclopramide) Tablets/ODT/Injection." *Id.*

[34] *Medication Guide Reglan*, U.S. FOOD AND DRUG ADMIN. (June 2009), http://www.fda.gov/downloads/Drugs/DrugSafety/UCM176362.pdf

[35] "FDA has determined that Reglan (metoclopramide) Tablets/ODT/Injection have serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Reglan (metoclopramide) Tablets/ODT/Injection."

Many other examples have been reported of pharmaceuticals once thought to be reasonably safe and effective, but later recognized to present safety issues warranting their withdrawal or labeling modification.[36] Prerequisite to the proper functioning of this safety system is the willing and active participation by all members of the health-care community, including those who manufacturer and sell generic drugs.

"[W]ith regard to manufacturers of pharmaceuticals, most jurisdictions recognize a 'continuous duty' to remain apprised of new scientific and medical developments and to inform the medical profession of pertinent information related to treatment and side effects."[37] Hence, this duty is not passive, but requires ongoing diligence by the drug maker. This duty is fairly characterized as a "modest duty"[38] and one that flows from the recognition that a

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U.S. FOOD AND DRUG ADMIN., http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM111376.pdf (last visited 2/25/2011).

[36] *See, e.g.*, Wysowski, D., *Adverse Drug Event Surveillance and Drug Withdrawals in the United States 1969-2002: The Importance of Reporting Suspected Reactions*, 165 ARCH. INT'L. MED. 1363-69 (2005); Gostin, L., *The Deregulatory Effects Of Preempting Tort Litigation: FDA Regulation Of Medical Devices*, 299(19) J. AM. MED. ASS'N 2313-16 (May 21, 2008).

[37] Ross, K., *Post Sale Duty to Warn, A Report of the Products Liability Committee*, AM. BAR ASS'N, SECTION ON LITIGATION, at 13 (2004), http://www.productliabilityprevention.com/images/5-PostSaleDutytoWarnMonograph.pdf.

[38] Brief of the United States of America as Amicus Curiae, at 22.

pharmaceutical manufacturer "is held to the knowledge and skill of an expert; the manufacturer's status as expert means that at a minimum he must keep abreast of scientific knowledge, discoveries, and advances and is presumed to know what is imparted thereby."[39]

The inherent validity and necessity of a shared, affirmative duty of brand name and generic drug manufacturers to monitor drugs for safety is evidenced by the fact that the appellate courts addressing this issue have all held that such a duty is required by law and is consistent with congressional intent.[40] Similarly, commentators and policy makers do not distinguish between brand and generic manufacturers in finding a "continuing duty to keep abreast of scientific developments affecting the manufacturer's product and warn the medical community of any newly discovered risks."[41] The overriding importance of this

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[39] *Foster v. Am. Home Prods.*, 29 F.3d 165, 170 (4th Cir. 1994), citing *Owens-Illinois v. Zenobia*, 325 Md. 420, 601 A.2d 633, 639 (Md. 1992) (quoting *Borel v. Fibreboard Paper Prods. Corp.*, 493 F.2d 1076, 1098 (5th Cir. 1973), *cert. denied*, 419 U.S. 869 (1974)).

[40] *Gaeta v. Perrigo Pharms. Co.*, No. 09-15001, 2011 WL 198420, at *1 (9th Cir. Jan. 24, 2011); *Demahy v. Actavis, Inc.*, 593 F.3d 428, 430 (5th Cir. 2010), *cert. granted*, 78 U.S.L.W. 3745 (U.S. Dec. 10, 2010) (No. 09-1501); *Mensing v. Wyeth, Inc.*, 588 F.3d 603, 607 (8th Cir. 2009), *cert. granted*, 78 U.S.L.W. 3522 (U.S. Dec. 10, 2010) (No. 09-993), *and cert. granted*, 78 U.S.L.W. 3523 (U.S. Dec. 10, 2010) (No. 09-1039).

[41] Ross, K. and Prince, D., *Post-Sale Duties*, 74 BROOK. L. REV., 963, 982 (2009), http://productliabilityprevention.com/images/BLS_PrinceandRoss_vol74.3,2009.pdf; *see also* Gastwirth, J., *The Need for Careful Evaluation of Epidemiological Evidence in*

watchful, dynamic approach to pharmacovigilance cannot be overstated.

Pharmacovigilance has evolved from a fragmented and unreliable data accumulation mechanism to become an important tool in formulating global health-care policy. The World Health Organization has often taken the initiative in advocating a coordinated global pharmacovigilance network. This venerable authority has declared:

> The principle [of product stewardship] requires pharmaceutical manufacturers to assume responsibility for the impact of their activities "from cradle to grave", including consideration of the key influences in regulatory, customer and community contexts. . . . Responsibility for their products extends to all manufacturers (including those who produce generic medicines) and suppliers of raw materials. More broadly,

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Product Liability Cases: a Reexamination of Wells v. Ortho and Key Pharmaceuticals, 2 LAW, PROBABILITY AND RISK 151-189 (2003), http://lpr.oxfordjournals.org/content/2/3/151.full.pdf; Reid, M., *Comment, Vermont Supreme Court Rules That Food and Drug Administration Regulations Do Not Preempt State Failure-to-Warn Claims: Levine v. Wyeth*, 4 J. HEALTH & BIOMEDICAL L. 413, 425 (2008); Zellmer, S., *Preemption by Stealth*, 45 HOUS. L. REV. 1659, 1694-95 (2009); Vladeck, D., *The FDA and Deference Lost: A Self Inflicted Wound or the Product of a Wounded Agency? A Response to Professor O'Reilly*, 93 CORNELL L. REV. 981 (2008) ("Vladeck"), http://www.lawschool.cornell.edu/research/cornell-law-review/upload/Vladeck.pdf; Noah, L., *Platitudes About "Product Stewardship" in Torts: Continuing Drug Research and Education*, 15 MICH. TELECOMM. AND TECH. L. REV. 359 (2009), http://www.mttlr.org/volfifteen/noah.pdf; Ramey, *supra* note 14.

> the idea of stewardship is applicable to all industries.[42]

This policy declaration – in which all drug manufacturers are vested with responsibility for "product stewardship" – echoes the pharmacovigilance dictates of other developed countries. The Medical Associations' review of the available resources reveals that the developed nations of the world recognize that all drug makers – including those who manufacture generic drugs – share the burden of actively and responsibly monitoring the safety of marketed drugs.

The Canadian Generic Pharmaceutical Association voiced its posture on this issue in a statement to the House of Commons, explaining that "[a]ll pharmaceutical companies in Canada are required to monitor the use and effect of a given medication, and to detect, assess, understand and prevent any adverse reactions or any other medicine-related problems that arise."[43] This pharmacovigilance includes "ongoing monitoring and literature reviews on a global basis to identify any adverse drug reaction case reports."[44] As to a distinction between innovator and generic drugs:

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[42] *The Importance of Pharmacovigilance: Safety Monitoring of Medicinal Products*, WORLD HEALTH ORG. OFC. OF PUBLICATIONS, at 32 (2002), http://apps.who.int/medicinedocs/pdf/s4893e/s4893e.pdf.

[43] *Presentation to the House of Commons Standing Committee on Health: Study on Post Market Surveillance*, CANADIAN GENERIC PHARM. ASS'N, 1 (Feb. 5, 2008), http://www.canadiangenerics.ca/en/news/docs/post-market_surveillance_English.pdf.

[44] *Id.* at 2.

"Post-marketing risk management activities should be identical for both brand-name and generic products. This is the current practice and it should continue."[45] Thus, in Canada, the "generic pharmaceutical industry remains committed to good pharmacovigilance practice, and to working collaboratively with both domestic and international health authorities and other stakeholders to minimize public risk and ensure the safe use of generic drugs."[46]

In Europe, both brand and generic drug manufacturers are subject to the "The Rules Governing Medicinal Products in the European Union, Volume 9A -- Pharmacovigilance for Medicinal Products for Human Use."[47] The European Generic Medicines Association likewise validates the importance of ongoing and comprehensive drug safety surveillance, declaring "it is important to assess on a permanent basis that the risk-benefit of a given

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[45] *Id.* at 3.

[46] *Id.*

[47] "The pharmacovigilance obligations apply to all medicinal products authorized in the EU, including those authorized before 1 January 1995 and whatever procedure was used for their authorization. For example, the obligations are the same for products authorized under Articles 10(1), 10(4), 10a, 13 to 16 and 16a to 16i of Directive 2001/83/EC ('generic', 'similar biological medicinal product', 'well-established use', 'homeopathic' and 'herbal' products respectively) as for products authorized under Article 6 of the same Directive." *Volume 9A of The Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use*, at 15, EUROPEAN COMM'N (Sept. 2008), http://ec.europa.eu/health/files/eudralex/vol-9/pdf/vol9a_09-2008_en.pdf.

medicine remains positive during its entire life cycle. Therefore monitoring the use and effect of medicines is an essential part of the activities of a pharmaceutical company."[48] The same rules appear to generally apply on the Asian continent.[49]

The international health-care community, including its members who manufacturer and sell brand and generic pharmaceuticals, recognize the necessity of a comprehensive, sophisticated, and active system of pharmacovigilance for all marketed drugs.[50] The United States has historically been a leader in this endeavor. It would be a disservice to the public and

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[48] *EGA Fact Sheet on Generic Medicines, Pharmacovigilance and Generic Medicines: Ensuring On-going Patient Safety*, EUROPEAN GENERIC MEDICINES ASS'N, http://www.egagenerics.com/doc/ega_factsheet-09.pdf. (last visited Feb. 16, 2011).

[49] "Both innovator and generic companies operate in Asia. An observation is that the pharmacovigilance regulatory expectations in the region do not distinguish between generic and innovator companies. Therefore, generics companies need to sustain the same level of compliance to these regulatory obligations as much as their innovator counterparts." Sharma, V., *Pharmacovigilance: Playing by the Rules*, PHARMAASIA (June 1, 2009), http://www.pharmaasia.com/article-7805-pharmacovigilanceplaying bytherules-asia.html; *see also* Du, W., *et al.*, *Drug Safety Surveillance in China and Other Countries: A Review and Comparison*, 11 INT'L SOC. FOR PHARMACOECONOMICS AND OUTCOMES RESEARCH S130–36 (2008), http://www.ispor.org/consortiums/asia/ViH/19-Guo.pdf.

[50] *See, e.g.*, WHO COLLABORATING CENTRE FOR INTERNATIONAL DRUG MONITORING, THE UPPSALA MONITORING CENTRE, http://www.who-umc.org (last visited Feb. 25, 2011); *see also* INTERNATIONAL SOCIETY OF PHARMACOVIGILANCE, http://www.isoponline.org (last visited Feb. 25, 2011).

the health-care community to retreat from the progress made in this arena.

C. Principles of Federalism and Constitutional Recognition of States' Rights Warrant Respect for Local Health-Care Policy

In view of the foregoing arguments, it is difficult to fathom the basis for a policy declaration that excuses a critical member of the health-care community from active and responsible participation in the process of pharmacovigilance. We begin with the concepts espoused by *Levine*, dictating that one must first examine the "purpose of Congress" bearing in mind that "the historic police powers of States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress."[51] Amici Curiae concur that federal preemption of local health-care laws and regulations is generally disfavored and unwarranted. Thus, what is the countervailing policy argument?

Petitioners go to great lengths to dissect and analyze the FDCA, its empowering regulations and provisions, and FDA pronouncements. The single goal of this exercise is to create the appearance of a conflict upon which they may base an argument for preemption of the affirmative and continuing responsibility for the safety of drugs they sell. The generic drug makers urge that Congress and the FDA both had "the vision" to "place the burden of

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[51] *Levine*, 129 S. Ct. at 1195 (quoting *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996)).

prescription drug labeling content on the branded drug manufacturer and the FDA...."[52] The industry minimizes its role in pharmacovigilance, proposing that it need only report adverse events they actually receive or reports they "happen to hear about."[53] This passive approach to drug safety would undermine the entire notion of responsible, valid surveillance. Finally, the industry seeks to excuse its members from active surveillance of a key source of adverse event data – the scientific literature - stating that "such a requirement would only increase costs to no meaningful end."[54] These arguments arise from a tangled interpretation of the applicable drug laws, which ultimately would disserve the patients and the medical community this industry was created to serve. Moreover, this construction obfuscates and undermines clear monitoring and reporting mandates.[55]

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[52] Petitioner Pliva's Reply Brief at 1; Brief of Petitioner Actavis at 20.

[53] Brief of Petitioner Pliva at 19.

[54] Amicus Brief of Generic Pharmaceutical Association at 19. Of note, Petitioner Actavis construes the FDA regulations to require that the medical literature be monitored. *See* Brief of Petitioner Actavis at 6: "A generic manufacturer is required to report adverse drug experiences that it 'obtain[s] or otherwise receive[s]' from any source, including scientific literature, and to submit new safety information in its annual report to FDA."

[55] Generic manufacturers must follow the same rules for record keeping and reporting of adverse drug experiences that name brand manufacturers must follow (21 C.F.R. § 314.98), which includes reports from the scientific literature (21 C.F.R. § 80(c) and (d)). This information requires communication with the FDA if it reveals "reasonable evidence of an association of a serious

Wyeth v. Levine[56] provides the guideposts for disposition of the current appeal. First, the one hundred year history of food and drug law in the United States manifests a clear congressional intent that such laws are designed to "protect the public health" and "assure the safety, effectiveness, and reliability of drugs" while taking care "to preserve state law."[57] The various amendments to the Food and Drug act all evidence a national policy to "bolster consumer protection against harmful products."[58]

Second, legislative action, as well as inaction, on the issue of express preemption statutes provides "powerful evidence that Congress did not intend FDA oversight to be the exclusive means of ensuring drug safety and effectiveness."[59] Thus, "the longstanding coexistence of state and federal law and the FDA's traditional recognition of state law remedies" buttress the conclusion that "state law offers an additional, and important, layer of consumer protection that complements FDA regulation."[60]

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hazard with a drug." (21 C.F.R. § 201.57(c), now re-designated as 21 C.F.R. § 201.80(e)).

[56] *Levine*, 129 S. Ct. 1187.

[57] *Id.* at 1195-96.

[58] *Id.* at 1199.

[59] *Id.* at 1200.

[60] *Id.* at 1202.

Finally, in view of the "demanding" nature of the defense of impossibility preemption,[61] it is difficult to envision that Congress nonchalantly, and without discussion, modified the comprehensive nature of the national system of pharmacovigilance by happenstance.[62] *Levine* also places the burden of proof on the proponent of this defense to establish that the FDA would have refused to approve a proposed labeling change or other proposal to convey improved safety information.[63] Absent in this case is the "clear and manifest purpose of Congress"[64] that the law demands to excuse an industry from its duty to serve as a vigilant, dynamic, and responsible member of the health-care community.

The appellate courts addressing the issue sought to respect congressional mandates while demanding a sensible construction and interpretation of the applicable laws and regulations. The challenge presented is that our system of pharmacovigilance arises from a morass of laws, regulations, and interpretations that provide less than optimal guidance to the courts, and that are subject to misinterpretation. The regulations and guidelines

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[61] *Id.* at 1199.

[62] "[T]he legislative history for the [Hatch-Waxman] act does not contain any signal that either brand name or generic manufacturers ever considered its liability implications." Ramey, *supra* note 14, at 91-92; *see also* Vladeck, *supra* note 41, at 986 n.29.

[63] *See id.* at 1198-99.

[64] *Levine*, 129 S. Ct. at 1195.

offer alternative methods of revising labels and disseminating product safety information. It should be demanded that generic drug makers select the most appropriate and timely vehicle by which important drug safety messages may be communicated to those who need and rely upon this information. Hence, the courts in *Mensing*, *Demahy*, and *Perrigo* clearly recognized the foundation for a duty to affirmatively monitor pharmaceuticals and take action to protect the public health, while conscientiously seeking to identify the mechanisms by which such action may be accomplished. The common thread in these opinions is that, "at a minimum a generic manufacturer should alert the agency to any new safety hazard associated with its product," it should then "*provide adequate supporting information to the FDA*, and the FDA will determine whether the labeling for the generic and listed drugs should be revised."[65]

In *Levine*, this Court rejected an "untenable interpretation of congressional intent"[66] even more far reaching than the one advocated by Petitioners. The Court now stands positioned, once and for all, to

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[65] *Mensing*, 588 F.3d at 613 (emphasis in original); *Demahy*, 593 F.3d at 434 (emphasis in original); *see also Perrigo*, 2011 WL 198420, at *6. The United States as amicus curiae likewise supports the notion of a duty to notify FDA "[i]f an ANDA applicant believes new safety information should be added to a product's labeling...." Brief for the United States as Amicus Curiae at 15-16. The Medical Associations suggest that an interpretation of the FDA rules and regulations that diminishes the role of generic manufacturers in the scheme of pharmacovigilance would justifiably be viewed as "inherently suspect." *Levine*, 129 S. Ct. at 1190.

[66] *Levine*, 129 S. Ct. at 1199.

declare that drug safety and patient well being are national priorities and that all members of the health-care system play an important role in this effort. Amici Curiae urge the Court to take this crucial step.

D. The Current Appeal Has Significant Ramifications for the Safety of Generic Drugs and Responsibility for Patient Safety

A final issue of importance to the health-care community is the ramifications of this appeal on drug-prescribing behavior. Physicians must consider many factors in making health-care decisions, with their first priority being patient safety. Even so, physicians are faced with mounting pressure to be conscious of costs. Doctors should be entitled to prescribe an "equivalent" generic drug with assurance that it is truly the same as the brand, not only on the date of its approval, but during its lifetime on the market.

The selection of the optimal drug to prescribe implicates an assessment of its benefit-risk profile. Doctors make prescribing decisions based on the most current product safety information, not uncertain or unreliable safety data. Nonetheless, medical science evolves, and the benefit-risk information for drugs must remain dynamic.

Physicians customarily include in their informed consent discussion relevant information about "the risks and benefits of a proposed treatment or procedure" as well as "the risks and benefits of [any]

alternative treatment or procedure."[67] If alternative drug therapies are available, such as a generic equivalent, the physician may find it relevant to broach this subject with the patient.

Divergent liability rules for brand name and generic drugs pose an ethical dilemma for physicians. The medical profession recognizes the benefit of generic drugs and supports the right of physicians to select generic equivalents.[68] If a physician specifies that a prescription be filled with a brand name drug,[69]

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[67] *Patient Physician Relationship Topics: Informed Consent*, AM. MED. ASS'N, http://www.ama-assn.org/ama/pub/physician-resources/legal-topics/patient-physician-relationship-topics/informed-consent.shtml (last visited Feb. 16, 2011); *Code of Medical Ethics: Opinion 8.08 – Informed Consent*, AM. MED. ASS'N (2006), http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics/opinion808.shtml (Physicians have an obligation to "sensitively and respectfully disclose all relevant medical information to patients.").

[68] *See, e.g.*, *AMA Policy H-125.984*, *supra* note 4. It is beyond the scope of this brief to address the impact of the cost of medications on patient compliance and health, but researchers have found compelling evidence of a direct correlation between the two. *See, e.g.*, Goldman, D., *et al.*, *Prescription Drug Cost Sharing: Associations with Medication and Medical Utilization and Spending and Health*, 298(1) J. AM. MED. ASS'N, 61-69 (2007). It would be unfortunate indeed if patients had to choose between their pocketbook and their well-being.

[69] After the FDA approves a generic, the question of whether it is generically substitutable is a matter of state law. The states differ on how they determine which products are "generically equivalent." Some states have a "positive formulary" which lists all of the products which may be generically substituted in that state. Others have a "negative formulary" which lists those drugs – generally narrow therapeutic index ("NTI") drugs – that may not

he or she has an assurance that the drug company is monitoring the safety of the drug. Conversely, if the generic drug industry's argument prevails, there will be no guarantee that the product safety information accompanying a generic drug is current or reliable.

The scope of the problem under consideration is startling. The generic industry advises that 10,072 of the 12,751 drugs listed in the FDA's Orange Book[70] have generic counterparts and that generic pharmaceutical products are used to fill nearly 2.6 billion prescriptions every year. Generic medicines account for 69% of all prescriptions dispensed in the United States, and the industry is expected to grow at an annual rate of more than 7.8%, a pace that is faster than the world pharmaceutical market.[71] At what

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be substituted. And, others default to the FDA's determination of whether the product is bioequivalent. Carpenter, L. *Generic Substitution and Biopharmaceuticals: Where Are All the Follow-On Biologics? And, How Much Money Will They Save?*, NAT'L L. REV. (Jan. 1, 2010), http://www.natlawreview.com/article/generic-substitution-and-biopharmaceuticals-where-are-all-follow-bi. Texas law, for example, allows for generic substitution unless the patient expressly requests a brand name drug. *See, e.g.*, *What is a generic drug?*, TEX. ST. BD. OF PHARM. (2002-2004), http://www.tsbp.state.tx.us/consumer/broch3.htm.

[70] *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations*, U.S. FOOD AND DRUG ADMIN. (Jan. 2011), http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.

[71] *Facts at a Glance*, GENERIC PHARM. ASS'N (U.S.), http://www.gphaonline.org/about-gpha/about-generics/facts (last visited Feb. 25, 2011). These statistics may be understated. A recent news article on the prevalence of the use of generic drugs reported that as much as seventy-five percent of daily prescriptions are filled with generic substitutes. Herper, M.,

point this issue becomes a matter of patient safety is uncertain but what is certain is that this concern inevitably will arise.[72]

The safety of generic drugs will remain a prominent topic among patients and prescribers. The usual course in the drug industry is that a brand-name drug maker will monitor its product for as long as it has a financial interest and a legal obligation to do so. "[O]nce a manufacturer loses its exclusivity, it also loses its revenue stream."[73] The legal duty to monitor continues, but it is not uncommon for the brand maker to simply stop selling the drug when profits can no longer be realized.[74] If the generic drug makers' preemption argument wins the day, there may be no

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America's Most Popular Drugs, FORBES (May 11, 2010), http://www.forbes.com/2010/05/11/narcotic-painkiller-vicodin-business-healthcare-popular-drugs_print.html. Overall, only 8 of the 50 most popular drugs are still branded, compared to 20 in 2003, according to IMS Health. *Id.* This includes the top selling drug in the nation, Vicodin (a combination of hydrocodone and acetaminophen), which has recently been the subject of an FDA investigation culminating in the recommendation that the drug's continued use be banned. *See, e.g.*, Harris, G., *Ban is Advised on Top 2 Pills for Pain Relief*, N. Y. TIMES (July 1, 2009), http://www.nytimes.com/2009/07/01/health/01fda.html.

[72] As the court noted in *Demahy*, it would be a "bizarre conclusion" to determine that Congress intended to provide greater protection for patients who use brand name drugs compared to those who are prescribed generic drugs. 623 F.3d at 449.

[73] Ramey, *supra* note 14, at 87.

[74] *Id.* at 98. This article notes that, in the case of Reglan, the brand manufacturer reportedly assigned its rights and liabilities associated with the drug to Schwarz Pharma, Inc. in 2002.

one responsible for drug safety oversight for many popular and widely-prescribed drugs. Common sense and fairness dictate that this obligation be accepted by the product manufacturer.

The most important issue in this discussion remains patient safety. Physicians and their patients are entitled to a reasonable assurance that the drugs they use are safe and effective, for as long as they are on the market.[75] Pharmacovigilance is a comprehensive, vibrant, and continuing responsibility in which many parties play a role.[76] It is now accepted that brand name drug companies have an ongoing duty to actively monitor drugs they sell and to notify the FDA and/or revise the product labeling if warranted. It should be the responsibility of all drug makers to conduct reasonable and affirmative safety surveillance and to take appropriate action when significant safety concerns arise.

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[75] Many drugs are sold both in brand name and generic form. With as much as seventy-five percent (75%) of the drugs prescribed by physicians being generic products, it is critical that the safety of these drugs be monitored, just like the monitoring required of brand name drugs. *See, e.g.*, Herper, *supra* note 71.

[76] The AMA supports the broad policy that the FDA, the pharmaceutical industry, and physician organizations must collaborate and identify innovative ways to communicate new risk information about a drug or biological product to physicians so they will be aware of it, remember it, accept it, and act on it when prescribing a drug. *See, e.g.*, *AMA Policy H-125.984*, *supra* note 4.

CONCLUSION

The health-care system in the United States seeks to achieve a balance between competing factors, the most prominent of which is patient safety.[77] Even so, financial considerations cannot be ignored. The legislation authorizing the marketing of generic drugs was never meant to "pursue the objective of low-cost generic drugs without limitation."[78] "[T]he Hatch-Waxman Amendments were meant to provide an inexpensive and easy way for generic drugs to enter the market, they were not intended as a relief from the fundamental requirement of the FDCA that all marketed drugs remain safe."[79]

Health-care providers and their patients rightly expect that the drugs they use are reasonably safe and that their safety is being continually, aggressively monitored. The obligation for ongoing and affirmative safety surveillance lies with the party manufacturing the drug. The defense of "impossibility preemption" demands that the party seeking to avoid this obligation must affirmatively prove that the FDA would have refused to approve a proffered labeling change or other proposal to convey modified safety information to the public. Generic drug makers should

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[77] The Medical Associations respectfully present these arguments in view of the fact that this appeal "concerns a medical and scientific question of great importance: how best to save the lives of" all Americans. *See Bruesewitz v. Wyeth L.L.C.*, No. 09-152, 2011 WL 588789, at *13 (Feb. 22, 2011) (Breyer, J., concurring).

[78] Brief for the United States as Amicus Curiae, p. 20.

[79] *Perrigo*, 2011 WL 198420, at *11.

not be exempt from a duty to conduct continuous and affirmative pharmacovigilance of their products. If this surveillance reveals information relevant to the safety of their drugs, they should take action to assure that this information is communicated to prescribers and their patients. This responsibility may be fulfilled in any manner permitted by law but would include, at a minimum, furnishing adequate supporting information to the FDA, after which a determination may be made whether the product labeling should be modified. To do less would be an injustice to the public as well as the medical community.

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March 2, 2011

AMICUS CURIAE BRIEF

Nos. 09-993, -1039, -1501

In the Supreme Court of the United States

PLIVA, INC. ET AL.,
Petitioners,
v.
GLADYS MENSING,
Respondent.

ACTAVIS ELIZABETH, LLC,
Petitioner,
v.
GLADYS MENSING,
Respondent.

ACTAVIS, INC.,
Petitioner,
v.
JULIE DEMAHY,
Respondent.

On Writs of Certiorari to the United States Courts of Appeals for the Fifth and Eighth Circuits

BRIEF OF APOTEX, INC. AS *AMICUS CURIAE* IN SUPPORT OF PETITIONERS

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BRIEF OF APOTEX, INC. AS *AMICUS CURIAE* IN SUPPORT OF PETITIONERS

INTEREST OF THE *AMICUS CURIAE*[1]

Apotex, Inc. is the largest pharmaceutical company in Canada and a leading worldwide manufacturer and distributor of generic pharmaceuticals. Founded in 1974, Apotex manufactures approximately 300 generic drugs and sells those products worldwide. Apotex's customers include physicians, hospitals, and patients in the United States. Apotex has substantial experience dealing with the United States Food and Drug Administration ("FDA") and the federal statutes and regulations governing the approval and labeling of generic drugs. Accordingly, Apotex has a valuable perspective to contribute to this case as well as a substantial interest in the proper resolution of the important issue presented.

STATEMENT

A. The Hatch-Waxman Act and the Federal Regulatory Regime Governing the Labeling of Generic Drugs

1. The Drug Price Competition and Patent Term Restoration Act of 1984, known as the "Hatch-Waxman Act," modified the FDA approval process for

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[1] The parties' letters of consent to the filing of *amicus* briefs have been filed with the Clerk. Under S. Ct. Rule 37.6, *amicus curiae* states that no counsel for a party wrote this brief in whole or in part, and no counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person or entity, other than the *amicus curiae* or its counsel, has made a monetary contribution to this brief's preparation or submission.

generic drugs. A primary objective of the Act was "to make available more low cost generic drugs." H.R. REP. No. 98-857(I), at 14 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647, 2647. Thus, the Act established a framework designed to promote generic competition and speed the FDA approval process for generic drugs. See *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990).

Before the enactment of Hatch-Waxman, manufacturers seeking approval for generic versions of drugs that had been approved after 1962 were required to duplicate the expensive and time-consuming scientific and clinical studies already performed by the brand-name manufacturers. See H.R. REP. No. 98-857(I), at 16; H.R. REP. No. 98-857(II), at 2, *reprinted in* 1984 U.S.C.C.A.N. 2686, 2688; *Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193, 196 (2005); see also 21 U.S.C. § 355(a), (b) (setting forth new drug application ("NDA") process for brand-name drugs). The Hatch-Waxman Act eliminated that requirement. It authorized generic drug makers instead to file abbreviated new drug applications ("ANDAs") that relied on the same clinical safety and efficacy data that had been used to support the NDA. ANDA applicants need only demonstrate that the generic drug is bioequivalent to an approved brand-name drug. *Merck*, 545 U.S. at 196 n.1; *Eli Lilly*, 496 U.S. at 676; 21 U.S.C. § 355(j)(2)(A)(ii), (iv).

This new, streamlined review process speeds the FDA's approval of generic drugs and promotes generic competition. It also eliminates duplication of clinical studies. See *Eli Lilly*, 496 U.S. at 676; *Merck*, 545 U.S. at 196 n.1 (citing 21 U.S.C.

§§ 355(j)(2)(A)(ii), (iv), 355(j)(8)(B)). That, in turn, keeps generic drug manufacturers' costs down and allows them to offer generic drugs at a lower price, with significant benefits for consumers and for public health.

2. The abbreviated review process rests on the premise that generic drugs are pharmaceutically and therapeutically equivalent to their brand-name counterparts. To ensure that consumers and health-care professionals appreciate that equivalency, and are not dissuaded from using lower-cost generics based on a misimpression about differences in safety or efficacy, the Hatch-Waxman Act requires the labeling on every generic drug to be "the same as" the FDA-approved labeling for the drug's brand-name version. 21 U.S.C. § 355(j)(2)(A)(v); 21 C.F.R. § 314.94(a)(8)(iii); see also 21 U.S.C. § 355(j)(4)(G) (ANDA may be refused if the proposed labeling is not "the same as" that for the brand-name product); 21 C.F.R. § 314.127(a)(7) (same). Each ANDA must include a "side-by-side comparison" of the labeling for the generic drug and its brand-name equivalent (21 C.F.R. § 314.94(a)(8)(iv)) in order to "enable FDA reviewers to readily identify differences between the" two (57 Fed. Reg. 17,950, 17,961 (Apr. 28, 1992)).[2]

Even after receiving FDA approval, generic drug manufacturers have a continuing obligation to ensure that their labeling does not deviate from that employed by the brand-name manufacturer. Indeed, the FDA may withdraw approval of an ANDA if it

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[2] The statute and regulations do permit certain labeling variations not relevant here. 21 U.S.C. § 355(j)(2)(A), (C); 21 C.F.R. § 314.94(a)(8)(iv). Notably, additional warnings are *not* authorized. See also PLIVA Pet. Br. 12-14.

finds that the generic drug's labeling "is no longer consistent with that for the [brand-name] drug." 21 C.F.R. § 314.150(b)(10).

Should a generic drug maker determine that labeling changes to its product are warranted, it must seek FDA approval before implementing those changes. Generic drug manufacturers may not modify their products' labeling without prior agency approval. See 21 U.S.C. § 355(j); 21 C.F.R. § 314.70.[3] Instead, the manufacturer must "provide adequate supporting information to FDA," and FDA will then "determine whether the labeling for the generic *and* [brand-name] drugs should be revised." 57 Fed. Reg. at 17,961 (emphasis added).[4]

B. The Proceedings in the Lower Courts

These consolidated cases involve tort actions brought under state law against manufacturers of the generic drug metoclopramide ("MCP"), which is bioequivalent to the brand-name drug Reglan®. Plaintiffs in both cases alleged, among other things, that MCP's labeling was inadequate because it failed to provide adequate warnings concerning the risk of developing tardive dyskinesia ("TD"), a neurological movement disorder, from the long-term use of MCP.

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[3] Section 314.70 was revised in 2001. 69 Fed. Reg. 18,764 (Apr. 8, 2004), after the relevant events in *Mensing* v. *Wyeth*, 588 F.3d 603, 605 (8th Cir. 2009), but before the relevant events in *Demahy* v. *Wyeth*, 586 F. Supp. 2d 642, 643-44 (E.D. La. 2008). Neither the pre-2001 nor the post-2001 version of the regulation authorizes generic drug manufacturers to make labeling changes without FDA approval. Compare 21 C.F.R. § 314.70 (2001) with 21 C.F.R. § 314.70 (2008).

[4] For additional discussion of the federal generic-drug labeling scheme, see PLIVA Pet. Br. 12-20.

1. *Mensing* v. *Wyeth*. Between 2001 and 2005, respondent Gladys Mensing took MCP as prescribed by her physician to treat certain gastrointestinal disorders. After she developed TD, she brought suit against Wyeth, Inc., the manufacturer of Reglan®, and four manufacturers of MCP: petitioners Actavis Elizabeth LLC ("Actavis"), PLIVA, Inc., Teva Pharmaceuticals USA, and UDL Laboratories, Inc. Although Mensing advanced a variety of tort claims under Minnesota law, all of her claims targeted the defendants' alleged failure to provide adequate warnings.

The district court dismissed the failure-to-warn claims against the generic drug manufacturers on the ground that they were impliedly preempted by federal law. 562 F. Supp. 2d 1056 (D. Minn. 2008). The district court "conclude[d] that a generic drug manufacturer may not unilaterally strengthen a label without prior approval of the FDA." *Id.* at 1061-62. In particular, the court rejected Mensing's contentions that a generic manufacturer is free either (1) to alter its labeling "without prior approval of the FDA" through the "Changes Being Effected" ("CBE") regulation, 21 C.F.R. § 314.70(c), or (2) to send "Dear Doctor" or "Dear Health Care Provider" ("DHCP") letters to physicians and other providers. 562 F. Supp. 2d at 1063-65. The court also rejected Mensing's alternative argument that the generic manufacturers should have invoked the "prior approval supplemental [PAS] process under 21 C.F.R. § 314.70" by asking FDA to approve a global change to the labeling not only of MCP but also of Reglan®, explaining that the outcome of such a request was "uncertain and would require speculation as to what the FDA might have done." 562 F. Supp. 2d at 1065.

Relying on this analysis of the governing statute and regulations, the district court concluded that there was a direct conflict between Mensing's claim and the requirements of federal law:

> [U]nder the federal statutory scheme, the labeling for generic drugs must always remain the "same as" that of the name brand drug and . . . a generic drug manufacturer cannot unilaterally change its label without prior FDA approval. . . . Plaintiff's failure to warn claims . . . rely on state law imposing a duty on the generic drug manufacturers to provide adequate warnings that Actavis and Pliva allegedly did not provide. Any such duty to unilaterally heighten their warning labels, however, would directly conflict with the federal law requiring that their labels be the "same as" those of the listed drug, Reglan.

562 F. Supp. 2d at 1064-65. Indeed, the court further explained, "under these circumstances, it would be impossible for Actavis and Pliva to abide by both state and federal laws": the generic manufacturers "would be forced to choose between complying with the federal law while being exposed to state tort liability, or unilaterally adding a heightened warning to their labels at the risk of exposing themselves to federal liability." *Id.* at 1065. "This conflict," the court noted, would also "stand as an obstacle to the accomplishment and full purposes and objectives of the Hatch-Waxman Act, a key purpose of which is to increase the availability of low-cost generic drugs and to relax the generic approval and labeling process." *Ibid.*

The Eighth Circuit reversed the dismissal of the failure-to-warn claims against the generic manufac-

turers. 588 F.3d 603 (2009). That ruling was based, in large part, on the court of appeals' view that the generic manufacturers could have either proposed a labeling change through the PAS process or "suggested that the FDA send out a warning letter to health care professionals." *Id.* at 609-10. The Eighth Circuit also emphasized that "Congress could have crafted a preemption provision for generic drugs" as part of the Hatch-Waxman Act, but had failed to do so. *Id.* at 607. Finally, the court reasoned that *Wyeth* v. *Levine*, 129 S. Ct. 1187 (2009), required rejection of the preemption defense even though that case did not involve a generic drug or implicate the policies underlying the Hatch-Waxman Act. 588 F.3d at 607-12.

2. *Demahy* v. *Wyeth*. Between 2002 and 2006, respondent Julie Demahy took MCP manufactured by Actavis for the treatment of acid reflux. After she developed TD in 2007, Demahy brought suit in Louisiana state court against Wyeth and Actavis. After the lawsuit was removed to federal court and Wyeth was dismissed, Actavis moved to dismiss Demahy's state-law claims alleging that Actavis had failed to provide adequate warnings and had withheld information from the FDA concerning the hazards of MCP. The trial court granted the motion with respect to Demahy's fraud-on-the-FDA claim, which it held was preempted under *Buckman Co.* v. *Plaintiffs' Legal Committee*, 531 U.S. 341 (2001), but denied the motion with respect to the failure-to-warn claim. 586 F. Supp. 2d 642, 645-46 (E.D. La. 2008).

The Fifth Circuit affirmed. 593 F.3d 428 (2010). In concluding that Demahy's failure-to-warn claim was not preempted, the court opined that neither the

Hatch-Waxman Act nor FDA's labeling regulations prevented Actavis from altering its generic drug labeling either unilaterally through the CBE process, or (following approval by FDA) either through the PAS process or by sending "Dear Doctor" letters. *Id.* at 444-45. Relying on that understanding of the federal regulatory scheme, the Fifth Circuit rejected Actavis's conflict preemption argument. *Id.* at 445-49. Like the Eighth Circuit, the Fifth Circuit relied heavily on – and declined to distinguish – *Wyeth* v. *Levine*. 593 F.3d at 433-34, 445-46.

C. The Acting Solicitor General's Invitation Brief

After petitions for certiorari were filed seeking review of the Eighth Circuit's decision in *Mensing* v. *Wyeth* (Nos. 09-993 and -1039), this Court invited the Solicitor General to file a brief expressing the views of the federal government (including the FDA). 130 S. Ct. 3349 (2010) (order).

Although urging this Court to deny the petitions, the Acting Solicitor General's brief acknowledged that the Eighth Circuit in several respects had seriously misunderstood the federal regulatory regime governing the labeling of generic drugs. Nos. 09-993 & -1039 U.S. Br. 10, 11, 13, 17. *First*, the Eighth Circuit had "incorrectly concluded that the PAS process was intended for" the use of generic manufacturers, when in fact that process "was not expressly available to any manufacturer to change approved labeling to add or strengthen a warning." *Id.* at 11, 13; see also *id.* at 14-15 (labeling changes relating to "added or strengthened warnings" were "not intended to be made through the PAS process"). *Second*, the Eighth Circuit had "misunderstood the

status of DHCP letters." *Id.* at 17. Generic drug manufacturers, the government explained, "do not customarily send" Dear Doctor or DHCP letters "without coordinating with FDA." *Id.* at 17-18. Moreover, if such a letter warned about "risks seemingly unique to its product" (as respondent Mensing "seems to envision" should have been sent in this case), the letter "would likely be misleading" because it "could mislead consumers and providers into believing that the generic drug" and branded drug "were not therapeutic equivalents." *Ibid.*; see also *id.* at 13 (explaining that sending the Dear Doctor letters sought by Mensing "could have resulted in misbranding the drug" in violation of federal law). Finally, with respect to the *third* potential route for labeling changes claimed by Mensing — the CBE regulation — the government confirmed that the district court was correct in concluding "that the CBE process" was also "unavailable to petitioners." *Id.* at 11; see also *id.* at 13. Although the Eighth Circuit "did not disturb that holding," *id.* at 13, the Fifth Circuit in *Demahy* v. *Actavis* built its analysis in part on the flawed contrary assumption that a generic manufacturer *could* use the CBE process to make unilateral changes to the MCP labeling, *id.* at 22 n.10.

The government's description of how the federal statutory and regulatory regime operates — based on FDA interpretations that the Acting Solicitor General contends are entitled to receive *Chevron* deference, *id.* at 13 — confirmed the fundamental premise of petitioners' preemption argument: that "federal law required them to maintain labeling for their generic drugs that was the same as the labeling of the" branded equivalent, and a generic manufacturer "is

not free to change its approved labeling at will." *Id.* at 11-13; see also *id.* at 13 (a generic manufacturer "may not unilaterally change its approved labeling"). Nevertheless, the government suggested that Mensing's "failure-to-warn claims" may not be "*categorically* preempted" (*id.* at 11 (emphasis added)) because (1) their maintenance would not frustrate the purposes underlying the Hatch-Waxman Act, and (2) as the Eighth Circuit had suggested, a claim that the generic manufacturer should have communicated risk information to the FDA and urged the FDA to approve a global labeling change or a Dear Doctor letter would not be preempted. *Id.* at 18-22. Lastly, the government agreed with the Eighth Circuit that, in litigation over such a "failure-to-inform-the-FDA-and-request-a-labeling-change" claim, it would be "reasonable" to place the burden on the defendant to prove that the FDA would *not* have approved the labeling change if one had been sought. *Id.* at 19.

INTRODUCTION AND SUMMARY OF ARGUMENT

These cases present the question whether federal law — in particular, the Hatch-Waxman Act's command that a generic drug's labeling be "the same as the labeling approved for" the brand-name drug equivalent (21 U.S.C. § 355(j)(2)(A)(v), (4)(G)) — impliedly preempts a state-law requirement that the generic drug's manufacturer use labeling that is *not* "the same as" the brand-name drug's. In rejecting the preemption defense, the Fifth and Eighth Circuits misread *Wyeth* v. *Levine*, profoundly misunderstood the relevant federal drug-labeling regulations, and misapplied longstanding principles of federal

preemption law. They also overlooked critical distinctions between the regulatory regimes governing generic and brand-name drugs. As a result of these errors, the courts below failed to recognize that the state-law requirements underlying respondents' tort claims are preempted for at least three reasons: it is impossible for manufacturers to comply with them while at the same time obeying the federal labeling requirements set forth in the Hatch-Waxman Act and in the FDA's related regulations; they squarely conflict with those federal requirements; and finally, if left unpreempted, they would frustrate Congress's central purpose in enacting Hatch-Waxman, which was to ensure the broad availability of affordable generic medications.

1. The lower courts' decisions reflect several fundamental misunderstandings about the doctrine of conflict preemption. As this Court has repeatedly recognized, that doctrine is of vital importance to the constitutional scheme, and all three of the variants of conflict preemption implicated in this case — impossibility, obstacle, and "ordinary" conflict preemption — have deep roots in the Supremacy Clause and in this Court's preemption decisions.

Nevertheless, the Fifth and Eighth Circuits apparently are of the view that, in cases concerning generic drug labeling, federal law cannot impliedly preempt state-law tort requirements because Congress failed to include an express preemption clause in the Hatch-Waxman Act. That reasoning is unsound. Whenever it legislates, Congress acts against the backdrop of the well-established principles of conflict preemption, which are assumed, in every instance, to protect federal laws from

conflicting state requirements. Contrary to the lower courts' opinions, *Wyeth* v. *Levine* does not direct otherwise. In *Levine*, this Court observed, with respect to brand-name drugs, that federal oversight is not "the exclusive means of ensuring drug safety and effectiveness." 129 S. Ct. at 1200. But it certainly did *not* direct that, whenever Congress has not expressly preempted state law in this field, state-law requirements must prevail, even when they are directly contrary to and interfere with the fundamental objectives of federal legislation.

In addition to misunderstanding this Court's discussion of preemption in *Levine*, each court of appeals below overlooked crucial differences between the case before it and *Levine*. These consolidated cases involve a federal statute (and its implementing regulations) that mandate national uniformity in labeling between branded drugs and their generic equivalents. In this case, unlike *Levine*, federal law mandates that generic drug manufacturers maintain labeling that is "the same as" the FDA-approved labeling of the bioequivalent brand-name drug. 21 U.S.C. § 355(j)(2)(A)(v), (4)(G). And, unlike the brand-name drug manufacturer in *Levine* (which was governed by a different set of federal regulations), petitioners here have fewer mechanisms available to them for bringing about changes to their products' labeling. (Indeed, they may take no action without explicit FDA approval.) Finally, because *Levine* involved only brand-name pharmaceutical products, that case did not implicate the congressional purposes underlying the Hatch-Waxman Act, which include promoting competition for generic drugs and ensuring that consumers understand that such drugs

are in fact bioequivalent to their brand-name counterparts.

II. The Fifth and Eighth Circuits also failed to appreciate that state-law requirements such as those respondents seek to enforce – mandating that generic drug manufacturers unilaterally modify their labeling (or suggest new labeling) incorporating new safety information – would fundamentally frustrate Congress's effort to promote competition for generic drugs. Because generic drug manufacturers do not conduct clinical trials or studies on drug safety and efficacy, they never acquire the knowledge base enjoyed by the brand-name drug manufacturer and the FDA. As a result, unlike their branded counterparts, they cannot make meaningful judgments to support new labeling proposals – at least not without replicating the costly and time-consuming research efforts previously undertaken by the brand-name manufacturers. And if, contrary to Congress's intent, generic drug manufacturers *were* required to duplicate brand-name manufacturers' efforts in order to satisfy their state tort-law obligations, they would be unable to bring their products to market as quickly or at as low a cost as the Hatch-Waxman Act envisioned.

III. In its decision below, the Eighth Circuit proposed a preemption regime in which generic drug manufacturers may still be held liable for failing to (1) inform the FDA of new safety information, and (2) "take steps" to obtain a labeling change incorporating that information. 588 F.3d at 608, 611. Such a claim would be preempted, the Eighth Circuit held, only if the manufacturer could prove that FDA officials would have decided *not* to direct a requested

change to the drug's labeling. *Id.* at 610-11. That proposal is completely unworkable in practice as well as fundamentally inconsistent with *Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341 (2001). Much like the fraud-on-the-FDA claims this Court found impliedly preempted in *Buckman*, the unorthodox state-law claims envisioned by the Eighth Circuit would inappropriately interfere with the relationship between a federal regulatory agency and the entities it regulates. Moreover, as in *Buckman*, the proposed liability framework has the potential to create significant operational difficulties for the FDA. Just as the Solicitor General (speaking for the FDA) argued in *Buckman*, here too the maintenance of these state-law claims would threaten to delay agency action and harm both competition and the delivery of medical care.

ARGUMENT

Respondents' state-law claims are preempted by the federal generic-drug labeling requirements in the Hatch-Waxman Act and FDA regulations. Because the Fifth and Eighth Circuits committed numerous critical legal errors when reaching contrary conclusions, the decisions below should be reversed.

I. THE FIFTH AND EIGHTH CIRCUITS MISUNDERSTOOD AND MISAPPLIED FUNDAMENTAL, LONGSTANDING PRINCIPLES GOVERNING THE DOCTRINE OF IMPLIED PREEMPTION

As the government's invitation brief at the petition stage demonstrates, the Fifth and Eighth Circuits, in rejecting the preemption defense, relied on a misunderstanding of the federal statutes and

regulations governing generic-drug labeling. Both courts of appeals also profoundly misunderstood how the FDA has long interpreted and administered those statutory and regulatory provisions. As fundamental as those errors were, however, they were not the only reasons why both courts of appeals went astray. As we next explain, the flawed decisions below were also predicated on fundamental misunderstandings concerning the doctrine of implied preemption, including the meaning of *Wyeth* v. *Levine*, 129 S. Ct. 1187.

A. The Doctrine Of Conflict Preemption Is An Indispensable Part Of The Constitutional Scheme

Contrary to the apparent assumption of the Fifth and Eighth Circuits, federal preemption of state and local law is an ordinary, intended, and indispensable feature of the constitutional scheme. Congress's authority to legislate *preemptively* (rather than concurrently with sub-national governments) is "[a] fundamental principle of the Constitution." *Crosby* v. *National Foreign Trade Council*, 530 U.S. 363, 372 (2000). Congress so legislates using its powers enumerated in Article I of the Constitution, including the Necessary and Proper Clause, U.S. CONST. art. I, § 8.[3]

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[3] This constitutional basis is important because it explains why the exercise of preemptive authority by Congress raises no concern under the Tenth Amendment, which provides that "[t]he powers not *delegated* to the United States by the Constitution, nor prohibited by it to the States, are *reserved* to the States respectively, or to the people." U.S. CONST. amend. X (emphasis added). As this Court has explained, "[i]f a power is delegated to Congress in the Constitution, the Tenth Amendment expressly disclaims any reservation of that power to the States; if a power is an attribute of state sovereignty reserved by the Tenth

In many statutes covering a wide array of subjects, Congress has elected to include provisions that expressly preempt state and local law. More importantly for present purposes, Congress's handiwork — and other federal laws, including duly promulgated agency regulations — have a preemptive effect on inconsistent state and local laws even in the absence of such "express" preemption provisions.

This result flows directly from the Supremacy Clause of the Constitution, which provides: "This Constitution, and the laws of the United States . . . and all Treaties . . . shall be the supreme Law of the Land; and the Judges in every State shall be bound thereby, any Thing in the Constitution or Laws of any State to the Contrary notwithstanding." U.S. CONST. art. VI, cl. 2. State and local laws that conflict with federal law are preempted "by direct operation of the Supremacy Clause." *Brown* v. *Hotel & Restaurant Employees & Bartenders Int'l Union Local 54*, 468 U.S. 491, 501 (1984). The Framers included the Supremacy Clause to remedy glaring shortcomings in the Articles of Confederation. *See Hughes* v. *Oklahoma*, 441 U.S. 322, 325 (1979) (the Framers believed that, "to succeed, the new Union would have to avoid the tendencies toward economic Balkanization that had plagued relations . . . among the States under the Articles of Confederation"). Moreover, the Framers chose to include the Supremacy Clause only after considering various other structural alternatives for ensuring federal supremacy. *See* No. 08-1314 Amicus Br. of the U.S.

Amendment, it is necessarily a power the Constitution has not conferred on Congress." *New York* v. *United States*, 505 U.S. 144, 156 (1992) (emphasis added).

Chamber of Commerce, *Williamson* v. *Mazda Motors*, at 21-25 (filed Sept. 28, 2010) (discussing this history). The Supremacy Clause reflected a decision by the Framers to entrust *the Judiciary* (rather than other institutions of government) with the responsibility, in the first instance, for ensuring that state and local laws that conflict with federal law shall be accorded no effect. *Id.* at 24-25.

This Court's decisions interpreting the Supremacy Clause – and articulating what has come to be known as the doctrine of implied conflict preemption – stretch back to the earliest days of the Republic. *See, e.g.*, *Gibbons* v. *Ogden*, 22 U.S. (9 Wheat.) 1 (1824); *Houston* v. *Moore*, 18 U.S. (5 Wheat.) 1 (1820); *M'Culloch* v. *Maryland*, 17 U.S. (4 Wheat.) 316 (1819). "[S]ince our decision in *M'Culloch*," the Court has explained, "it has been settled that state law that conflicts with federal law is 'without effect.'" *Cipollone* v. *Liggett Group, Inc.*, 505 U.S. 504, 516 (1992).

There are at least three variations or types of conflict preemption. This Court's precedents have separately discussed "'conflicts' that prevent or frustrate the accomplishment of a federal objective" (so-called "obstacle" preemption) and "'conflicts' that make it 'impossible' for private parties to comply with both state and federal law" ("impossibility" preemption). *Geier* v. *American Honda Motor Co.*, 529 U.S. 861, 873-74 (2000); *see also Wyeth* v. *Levine*, 129 S. Ct. at 1193-94, 1196-1204. In *Geier*, the Court refused to "drive[] a legal wedge" between the doctrines of obstacle and impossibility preemption, reaffirming its understanding that "both forms of conflicting state law are 'nullified by the Supremacy

Clause." 529 U.S. at 873-74. In addition to "impossibility" and "obstacle" preemption, the Court has long recognized and applied what might be called "ordinary" conflict preemption, under which the Supremacy Clause nullifies state and local laws that stand in conflict with requirements imposed by federal law.[1]

These doctrines of conflict preemption have been established for many years. For example, the Court's *test* for obstacle preemption has been the same for 70 years, and is derived from *Hines* v. *Davidowitz*, 312 U.S. 52, 67 (1941). The Supremacy Clause nullifies state or local law that "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." See also *Perez* v. *Campbell*, 402 U.S. 637, 649-50 (1971) ("Since *Hines* the Court has frequently adhered to this articulation of the meaning of the Supremacy Clause") (citing multiple cases). Moreover, the *doctrine* of obstacle preemption is much older than *Hines*, with deep roots extending back almost two centuries to this Court's earliest preemption decisions. See *Perez*, 402 U.S. at 649 (obstacle preemption has roots extending at least

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[1] See, e.g., *Buckman Co.* v. *Plaintiffs' Legal Committee*, 531 U.S. at 348 (state-law "fraud-on-the-agency" claims preempted because they "conflict with" the "delicate balance of statutory directives" that the FDA was charged with achieving in regulating medical devices); *Fidelity Federal Savings & Loan Ass'n* v. *de la Cuesta*, 458 U.S. 141, 148-49, 154-59 (1982) (state-law doctrine preempted because it conflicts with federal regulation). In contrast, the Eighth Circuit incorrectly treated conflict preemption as consisting of only obstacle and impossibility preemption. See *Mensing*, 588 F.3d at 608; accord *Gaeta* v. *Perrigo Pharmaceuticals Co.*, No. 09-1500, slip op. 1471, 1482 (8th Cir. Jan. 21, 2011) (making same mistake).

back to *Gibbons* v. *Ogden*, which recognized that state laws that "*interfere with*, or are contrary to the laws of Congress . . . ," are invalid under the Supremacy Clause") (quoting 22 U.S. (9 Wheat.) at 211) (emphasis added).[1]

Congress is presumptively aware of the settled backdrop of existing law – including the ordinary rules of conflict preemption that are applied to *all* statutes – whenever it legislates. *American Nat'l Red Cross* v. *S.G.*, 505 U.S. 247, 252, 260 (1992). For that reason, this Court on several occasions has cautioned that it is inappropriate to draw inferences from Congress's inclusion of an express preemption provision or savings clause in a federal statute about the effects such decisions might have on background principles of *implied* preemption. Thus, in *Freightliner Corp.* v. *Myrick*, 514 U.S. 280 (1995), the Court rejected the notion that Congress's inclusion of an express preemption clause "entirely forecloses any possibility of implied pre-emption." *Id.* at 288-89. And, more recently in *Geier*, this Court squarely rejected the argument that the proponent of a defense of conflict preemption must carry a "special burden" because of Congress's inclusion in the relevant statute of either an express preemption clause or a

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[1] *See also Houston*, 18 U.S. (5 Wheat.) at 22-24 (Supremacy Clause overrules state laws whenever their enforcement would "thwart[] or "oppose[] the "will of Congress," even if they do not contradict federal law); *M'Culloch*, 17 U.S. (4 Wheat.) at 427 (Marshall, C.J.) ("It is of the very essence of [federal] supremacy to remove all obstacles to its action within its own sphere . . .") (emphasis added); *Savage* v. *Jones*, 225 U.S. 501, 533 (1912) (a "state law must yield" if it prevents "the purpose of" a federal law from being accomplished or "frustrate[s]" the federal law's operation).

"savings" clause. 529 U.S. at 870-74. "Nothing in the statute," the Court there explained, "suggests Congress wanted to complicate *ordinary experience-proved principles of conflict pre-emption* with an added 'special burden.'" *Id.* at 870, 872, 874 (emphasis added). Instead, "ordinary conflict pre-emption principles" apply. *Id.* at 871; see also *id.* at 874 (same). So, too, here.

B. Congress's Failure To Include An Express Preemption Clause In The Hatch-Waxman Act Has No Bearing On Whether Conflict Preemption Bars Respondents' Claims

In rejecting the generic manufacturers' preemption defense, the Eighth Circuit attached significance to Congress's failure to include in the Hatch-Waxman Act an express preemption clause. "Congress could have crafted a preemption provision for generic drugs in its 1984 amendments," the court of appeals reasoned, "having done so for medical devices less than 10 years earlier" – yet Congress "chose not to do" so. *Mensing*, 588 F.3d at 607. The Fifth Circuit similarly relied on the absence of an express preemption provision in the Hatch-Waxman Act as a reason for rejecting the conflict-preemption defense. *Demahy*, 593 F.3d at 435.

This rationale does not withstand scrutiny. As noted above, the legal principles governing conflict preemption are well settled and of ancient lineage. At bottom, they represent this Court's longstanding interpretation of the Supremacy Clause. Whenever Congress enacts *any* statute, it does so against the backdrop of those long-settled principles, which are assumed automatically to apply to *every* federal law

to protect it against being nullified or subverted by state and local requirements. Once this basic truth is grasped, it should be obvious that the Congress need not ever include an express preemption provision in a statute unless it wishes to preempt a domain of state law that is *different* from what would be nullified through the ordinary operation of the doctrine of implied preemption. That is manifestly what Congress did in enacting the express preemption clause of the Medical Device Amendments ("MDA"), 21 U.S.C. § 360k(a), which preempts state tort requirements that are "different from, or in addition to," federal requirements even if they do not conflict (and further creates a method by which exemptions from preemption may be obtained from the FDA, see 21 U.S.C. § 360k(b)).

Nor were the Fifth and Eighth Circuits correct in suggesting that *Wyeth* v. *Levine* lends support to this rationale. See *Mensing*, 588 F.3d at 607; *Demahy*, 593 F.3d at 435. In *Levine*, this Court cited the example of the MDA's express preemption clause only in the limited context of evaluating the brand-name manufacturer's broad argument that permitting any state-law tort actions based on inadequate brand-drug labeling would thwart Congress's purpose underlying the FDCA that "FDA oversight . . . be the exclusive means of ensuring drug safety and effectiveness." 129 S. Ct. at 1200. The Court rejected that "interpretation of congressional intent" as "untenable," reasoning that Congress's principal goal was "to bolster consumer protection against harmful products." *Id.* at 1199. If Congress had truly intended "FDA oversight to be the exclusive means of ensuring drug safety and effectiveness," the Court explained, it would have taken action to limit

the alternative means of product liability actions. The Court in *Levine* manifestly did not say that Congress's failure to enact an express preemption clause reflects a desire to tolerate state and local laws that conflict with federal law.

If credited, the lower courts' broad reading of this language in *Levine* would place that case on a collision course with *Geier*, where the Court observed that it was difficult to believe that Congress, in enacting a federal statute, would "not have wanted ordinary pre-emption principles to apply where an actual conflict with a federal *objective* is at stake." 529 U.S. at 871 (emphasis added). To hold otherwise, the Court explained in *Geier*, would have the effect of "tak[ing] from those who would enforce a federal law the very ability to achieve the law's congressionally mandated objectives that the Constitution, through the operation of ordinary pre-emption principles, seeks to protect" – an outcome that "permits [the federal] law to defeat its own objectives, or ... destroy itself." *Id.* at 872 (internal quotation marks omitted). Here too, there is no good reason why Congress would have wanted to permit enforcement of state laws that would directly conflict with the requirements imposed by Hatch-Waxman or the congressional purposes underlying that statute.

The Fifth and Eighth Circuit's reliance on the absence of an express preemption provision in the Hatch-Waxman Act is especially perverse given that "Congress recognized the principles of conflict pre-emption in the FDCA," the statute that Hatch-Waxman amended. *Levine*, 129 S. Ct. at 1221 n.4 (Alito, J., joined by Roberts, C.J., and Scalia, J., dissenting) (citing Drug Amendments of 1962, Pub. L.

No. 87-781, § 202, 76 Stat. 780, 793 (1962) ("Nothing in the amendments made by this Act to the [FDCA] shall be construed as invalidating any provision of State law . . . unless there is a direct and positive conflict between such amendments and such provision of State law.")). By enacting that provision, Congress made clear that it did not intend to occupy the entire field of drug regulation; and Congress's reference to "direct and positive" conflicts — a shorthand for implied conflict preemption — clearly demonstrated both an awareness of, and an intent to *preserve*, the operation of conflict preemption. The Fifth and Eighth Circuits made no effort to reconcile their conclusions with this provision.

C. The Fifth And Eighth Circuits Misapplied This Court's Decision In *Wyeth* v. *Levine*

Although the Fifth Circuit acknowledged that "*Levine* is not the case before us," it nevertheless went on to rely heavily on that decision, which in its view "carr[ies] important implications" for the implied preemption defense of generic manufacturers. 593 F.3d at 433; see also *id.* at 434-35, 446, 449. The Eighth Circuit likewise was of the view that *Levine* "carries important implications" for this case. *Mensing*, 588 F.3d at 607.

The courts of appeals, however, simply failed to appreciate crucial distinctions between *Levine* and this case — and between the federal statutory and regulatory regime governing brand-name and generic drugs. In *Levine*, there was no federal statute mandating that the pharmaceutical manufacturer use labeling that was "the same as" the "labeling approved for" the bioequivalent drug by FDA (21

U.S.C. § 355(j)(2)(A)(v), (4)(G)). It is *that* federal-law command — missing in *Levine* — that is at the heart of petitioners' arguments based on ordinary conflict (as well as impossibility) preemption. Nor, as the government's invitation brief confirms, are the *regulatory* requirements imposed on generic manufacturers the same as those at issue in *Levine*. On the contrary, as the government explains, a generic manufacturer may *not* use the CBE regulation to make a change to its product labeling. In contrast, the brand-name manufacturer may use the CBE process to make such a change. It was precisely this capability — which generic manufacturers lack — that was the basis for rejecting the brand-name manufacturer's argument for impossibility preemption in *Levine*. This makes all the difference in the world.

The Fifth and Eighth Circuits also overlooked crucial differences between this case and *Levine* with respect to the manufacturers' *obstacle* preemption arguments. *Levine* did not involve the Hatch-Waxman Act and therefore did not in any way implicate the congressional purposes underlying that statute. Those purposes, of course, lie at the very heart of petitioners' obstacle preemption arguments, yet they had no bearing on the issue resolved in *Levine*. In other words, the maintenance of the failure-to-warn claim in *Levine* did not undermine Congress's objective of ensuring the uniformity of approved brand-name labeling and generic labeling (so that consumers would not be confused about the bioequivalence of generics and deterred from using them), did not undermine Congress's objective of reducing the cost of generic drugs for consumers (by freeing generic manufacturers from expensive

research and risk-analysis obligations), and did not implicate the FDA's regulatory commands designed to carry out these congressional objectives. The reason is simple: all of the congressional objectives were expressed in the Hatch-Waxman Act, which was in no way implicated in *Levine*.

Rather than credit these basic and dispositive differences between this case and *Levine*, the Fifth and Eighth Circuits seized on tertiary rationales and supporting reasons mentioned by this Court in passing or for quite limited purposes, and sought to elevate those points to broader legal principles that this Court's opinion does not fairly support (and that are inconsistent with other preemption decisions of this Court). As explained above, the Fifth and Eighth Circuits did that with respect to *Levine*'s mention of the absence of any express preemption clause dealing with brand-name drug labeling similar to the express preemption clause included in the MDA.

That is not the only example. The Eighth Circuit, for example, read *Levine* as establishing the general principle that "uncertainty about the FDA's response" to a manufacturer's request either to make alterations to its product labeling or to send out "Dear Doctor" letters "makes federal preemption less likely." *Mensing*, 588 F.3d at 610. But this Court in *Levine* hardly endorsed such a general principle. Instead, the Court treated skeptically the brand-name manufacturer's contention in *Levine* that, while it could unilaterally change its labeling under the CBE regulation, there was no guarantee that the FDA would not later reject it. It was in the context of rejecting that particular argument for impossibility preemption that this Court said what it said. Nor

could the Court have endorsed the broad principle attributed to it by the Eighth Circuit without creating a glaring inconsistency with other preemption decisions. For example, in *Buckman* v. *Plaintiffs' Legal Committee*, 531 U.S. 341, this Court held that fraud-on-the-FDA claims were impliedly preempted even though there was uncertainty as to whether the FDA would have approved the medical device in question in the absence of the alleged fraud. Yet that "uncertainty about the FDA's response" (388 F.3d at 610) in *Buckman* did not prevent this Court from ruling, unanimously, that the fraud-on-the-FDA claim was preempted. 531 U.S. at 343.

II. RESPONDENTS' CLAIMS ARE BARRED BY OBSTACLE PREEMPTION

Petitioners have persuasively demonstrated that respondents' failure-to-warn claims are preempted by both "impossibility" and "ordinary conflict" preemption. See PLIVA Pet. Br. 30-46; Actavis Pet. Br. 18-26. It was impossible for petitioners to obey the requirements respondents sought to impose on them through these state tort-law actions while at the same time obeying federal law (which required them to maintain labeling that was "the same as" that of the branded products). And the state-law requirement to alter the labeling and provide additional warnings directly and unambiguously conflicts with the federal prohibition on doing so. Although this case could be resolved on the basis of either impossibility or ordinary conflict preemption, petitioners also should prevail because the maintenance of respondents' claims would frustrate Congress's purposes in enacting the Hatch-Waxman Act.

With this legislation, Congress had two primary objectives. The first and most important was "to enable new drugs to be marketed more cheaply and quickly." *Eli Lilly*, 496 U.S. at 676. As previously explained, the Act accomplished that goal by authorizing generic drug manufacturers to file ANDAs, which "substantially shorten the time and effort needed to obtain marketing approval." *Ibid.* ANDA applicants may "avoid the costly and time-consuming studies" required for NDAs, by "substitut[ing] bioequivalence data for the extensive animal and human studies of safety and effectiveness." *Ibid.*; 21 U.S.C. § 355(j)(2)(A)(iv); compare 21 U.S.C. § 355(b)(1) (data submission requirements for brand-name manufacturers) and 21 C.F.R. § 314.50(d) (same). The Act's other objective was to encourage the development of new brand-name drugs. To that end, Congress extended patent terms for pioneer drugs, restoring some of the time lost on patent life during the pre-market approval process. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, § 201(a), 98 Stat. 1585 (codified at 35 U.S.C. § 156); H.R. Rep. No. 98-857(I), at 15.

The Hatch-Waxman Act thus reflects a careful balance between competition and innovation, easing barriers to entry for generic manufacturers, on the one hand, and extending brand exclusivity, on the other. See 57 Fed. Reg. at 17,951. Indeed, there is substantial evidence that the sponsors of the legislation regarded the provisions extending patent lives for brand manufacturers and relieving generic manufacturers from onerous research and testing requirements as a trade-off that benefited *both* industries as well as consumers and the overall

public health. See, e.g., 130 Cong. Rec. H24421-26 (Sept. 6, 1984). This carefully crafted balance would be fundamentally skewed – and a central purpose of Hatch-Waxman Act frustrated – if generic drug makers were required to obey state-law requirements such as those respondents seek to impose through the present tort actions.

Congress specifically intended to free up generic manufacturers from the need to conduct costly research studies and clinical trials required of brand-name manufacturers. Freed of that obligation to replicate research that has already been conducted, generic drugmakers are able to bring their products to market faster and at a far lower cost than their branded counterparts, just as Congress intended. Critically, however, because they do not conduct this expensive and time-consuming research, generic companies also lack the underlying scientific knowledge and clinical expertise of the brand-name manufacturers. For this reason, and (again) to avoid consumer confusion and misunderstanding that might deter use of generic drugs, the statute specifically limits generic drug makers' labeling obligations to ensuring that their products' labeling is "the same as" that for their branded equivalents. 21 U.S.C. § 355(j)(2)(A)(v); they must follow the lead of the innovators rather than independently develop and substantiate product warnings and safety information.

Unlike brand-name companies, generic drug makers also are not required to conduct extensive post-marketing research, including reviewing and analyzing all reported adverse drug events. Compare 21 C.F.R. § 314.80(b) (post-marketing reporting obli-

gations for NDA applicants) with *id.* § 314.98 (far less onerous requirements for ANDA applicants). Consequently, just as they lack the background knowledge to propose product labeling in the first instance, generic manufacturers also lack much of the information necessary to make meaningful scientific judgments about what, if any, labeling changes are warranted. Moreover, because they do not have access to the brand-name manufacturers' underlying scientific and clinical data – indeed, it seems unlikely that brand-name manufacturers would have any incentive to share such information with their generic competitors – generic manufacturers likely could not properly evaluate the significance of much of the adverse-event information they obtain.

The decisions below threaten to upend this regulatory framework. Not only would it run contrary to the federal scheme to require generic drug manufacturers to collect and analyze the vast amounts of information necessary to make substantive recommendations on drug labeling, but these obligations would pose the precise obstacles to competition that Congress sought to eliminate with the Hatch-Waxman Act. Generic manufacturers would be driven to make the same extraordinary investments in scientific and clinical research as brand-name companies – and thus would be unable to continue to offer their products at discounted rates. This, alone, would defeat one of the statute's primary objectives.

Nor is this all. Allowing individual juries to determine, on a case-by-case basis, generic drug manufacturers' labeling and reporting obligations would also thwart congressional objectives. The

approach taken by the Fifth and Eighth Circuits could cause generic drug makers to face a patchwork of varying – and possibly conflicting – state-by-state requirements relating to the labeling of their nationally distributed products. Such a regulatory regime would be extraordinarily burdensome (and costly) for the manufacturers and could create significant operational challenges for FDA officials at the receiving end of vastly differing sets of data (and labeling proposals) from generic manufacturers operating in different states. This would certainly interrupt the FDA's efficient review of information and it could result in a regime in which labeling for generic drugs regularly varied from State to State and deviated from that for branded products, in direct violation of federal law. Such a regime in turn would seriously undermine the Hatch-Waxman Act's goal of promoting competition between generic and brand-name drugs, as it is crucial to this goal that consumers and health-care professionals view generics and branded products as true equivalents. Consistent and uniform labeling as between generics and their brand-name equivalents eliminates confusion on this front and provides assurance that generics are as safe and effective as brand-name drugs. See 57 Fed. Reg. at 17,961.

III. THE EIGHTH CIRCUIT'S APPROACH IS UNWORKABLE AND INCONSISTENT WITH *BUCKMAN*

The Eighth Circuit characterized respondents' claims as resting on a theory that the generic drug manufacturers had "fail[ed] to *take steps* to warn their customers sufficiently of the risks from taking their drugs." *Mensing*, 588 F.3d at 611 (emphasis

added). The court also observed that, to avail themselves of a preemption defense in the district court, the generic drug manufacturers would have had to "show the likelihood of FDA *inaction*" on a proposal to modify their products' labeling. *Id.* at 610-11. In its petition-stage invitation brief, the government appeared to agree with the Eighth Circuit, suggesting that state-law failure-to-warn actions should not be "categorically preempted" by federal law at least where generic drug makers have declined to propose new warning language to the FDA in response to relevant new safety information. U.S. Br. 19-20. As explained below, however, this approach is both impractical and inconsistent with *Buckman Co.* v. *Plaintiffs' Legal Committee*, 531 U.S. 341.

1. As an initial matter, the state-law "take steps" claim posited by the Eighth Circuit does not implicate any presumption against preemption. In *Buckman*, which involved claims that a medical device manufacturer had fraudulently obtained FDA approval to market its product, the Court observed that "[p]olicing fraud against federal agencies is hardly 'a field which the States have traditionally occupied.'" *Id.* at 347 (quoting *Rice* v. *Santa Fe Elevator Corp.*, 331 U.S. 218, 230 (1947)). "To the contrary," the Court explained, "the relationship between a federal agency and the entity it regulates is inherently federal in character because the relationship originates from, is governed by, and terminates according to federal law." *Ibid.*

This analysis is equally applicable to the present case. Much like *Buckman*'s fraud-on-the-FDA claim, the Eighth Circuit's "failure-to-take-steps-to-inform

the-FDA" cause of action has shallow, if any, roots in "the historic primacy of state regulation of matters of health and safety." 531 U.S. at 348 (quoting *Medtronic, Inc.* v. *Lohr*, 518 U.S. 470, 485 (1996)). Accordingly, the presumption against preemption has no relevance here. This case thus stands in sharp contrast to *Wyeth* v. *Levine*, in which the Court found the presumption applicable when considering a well-established and long-standing state-law cause of action for failure to warn. See 129 S. Ct. at 1194-95.

2. The Eighth Circuit failed to appreciate that the claim it envisioned would invariably conflict with the FDA's enforcement of its own labeling and data reporting requirements. Here, too, *Buckman* is instructive. In that case, this Court looked to the "inherently federal" relationship between an agency and its regulated entities and noted the many ways in which "[t]he FDA is empowered to investigate suspected fraud" by those entities. 531 U.S. at 349. The Court concluded that state fraud-on-the-FDA tort actions would only impede the agency's ability to carry out its investigative responsibilities in a manner consistent "with the Administration's judgment and objectives." *Id.* at 350.

So too would a state-law "failure-to-take-steps-to-inform-the-FDA" claim impinge on an "inherently federal" relationship and threaten the agency's ability to enforce reporting requirements for generic drugs in the manner it chooses. The Hatch-Waxman Act requires that generic manufacturers keep records of and timely report to the FDA on their products' safety. 21 U.S.C. § 355(k). Each manufacturer must maintain a record of any "adverse event associated with the use of [its] drug," and periodically notify the

FDA of those events. 21 C.F.R. §§ 314.80(a), (c), 314.98(a). The FDA has at its disposal numerous mechanisms to ensure compliance with these requirements. For example, the agency may seek to withdraw ANDA approval if it finds that the applicant "has failed to establish" a record-keeping system "or has repeatedly or deliberately failed to maintain required records." 21 C.F.R. § 314.150(b)(1). Additionally, the FDA may withdraw approval and "prohibit continued marketing of the drug product" if the applicant fails to submit required reports to the agency. *Id.* §§ 314.80(g), 314.81(d). There is little reason to believe that these remedies are inadequate to ensure that the FDA receives the information it needs — or that state-law "failure-to-take-steps-to-inform-the-FDA" claims would do anything but disrupt the FDA's existing review mechanisms and enforcement decisions.

The Eighth Circuit's approach would also sow confusion. For example, it is unclear how much information generic manufacturers would need to submit to the FDA in order for their disclosures to be deemed adequate, under state tort law, for agency officials to determine whether to direct a drug-labeling change. To ensure the success of a preemption defense in "failure-to-take-steps-to-inform-the-FDA" litigation, drug makers would feel compelled to inundate the agency with potentially irrelevant information. They might submit any and all new safety-related data, even when the data presented no genuine concern. And each of a drug's sometimes dozens of generic manufacturers might feel obligated to survey scientific literature and pass on their findings to the FDA — even if the agency was simultaneously receiving the very same information

from the brand-name manufacturer. Agency officials would have to sort through this tsunami of additional – and likely irrelevant and redundant – information when determining which, if any, of it warranted a labeling change. All told, these claims could accomplish little more than overwhelming existing agency processes, distracting FDA officials, and diverting already limited agency resources.

3. The Eighth Circuit's proposal would also generate a host of additional problems arising from its requirement that, for a successful preemption defense, generic drug makers must prove the likelihood of agency *in*action. *See Mensing*, 588 F.3d at 611. This requirement could lead to highly intrusive discovery requests from parties seeking information about the FDA's internal processes.

Because the generic manufacturer is not part of the dialogue between the brand-name manufacturer and the FDA about a drug's safety and efficacy, the generic manufacturer would have little insight into what warnings and labeling information the agency had already considered and rejected. Accordingly, the only way a generic manufacturer could possibly demonstrate that the FDA would *not* have approved a warning sought by a plaintiff in a state tort-law action would be to submit extremely broad discovery requests to the FDA and seek testimony from agency officials on their deliberations and discussions with the brand-name manufacturer.

As the government has previously argued, such discovery requests impose unwelcome burdens on federal agencies, which is why the government takes the position that federal employees "are immune from third-party subpoenas issued in private litigation,"

that their testimony may be sought only "under an agency's *Touhy* regulations," and that an agency's refusal to allow its employees to testify "is subject to review only in federal court and only under the arbitrary or capricious standard of the Administrative Procedure Act." No. 06-1498 U.S. Br. 8, 21-23, *Warner-Lambert Co.* v. *Kent* (filed Nov. 28, 2007) (citations omitted); No. 98-1768 U.S. Br. 28-30, *Buckman Co.* v. *Plaintiffs' Legal Committee* (filed Sept. 13, 2000). The government's position has not been universally accepted by courts, however. See No. 06-1498 U.S. Br. 22. Where courts have rejected it, agency officials would be subjected, in litigation over "failure-to-take-steps-to-inform-the-FDA" claims, to hours of testimony regarding the actions they *might* have taken had they received new or different safety information. Where the government's position is accepted, an official's refusal to testify still would be subject to challenge under the Administrative Procedure Act. See *id.* at 22-23. And, in cases in which the FDA successfully argues that its internal deliberations are privileged, juries would be left only to guess about whether agency officials might have directed labeling changes had they received different information. See *id.* at 21-23.

In short, a rule such as that proposed by the Eighth Circuit could generate "widespread litigation . . . on whether testimony and other evidence could be secured from [the] FDA." No. 98-1768 U.S. Br. 29. In any event, under any of the above scenarios, a generic drug manufacturer's reporting obligations would be determined on a case-by-case basis by a jury that was merely speculating about what the FDA *might* have done in hypothetical circumstances. That is a recipe for unfairness and irrational outcomes. For all of

these reasons, the Eighth Circuit's proposal is unworkable in practice and threatens to hamstring the public-health mission of the FDA.

CONCLUSION

For the foregoing reasons, as well as those set forth by the petitioners in their briefs, the judgments of the Fifth and Eighth Circuits should be reversed.

Respectfully submitted.

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AMICUS CURIAE BRIEF

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In The
Supreme Court of the United States

PLIVA, INC., ET AL., PETITIONERS
v.
GLADYS MENSING, RESPONDENT

ACTAVIS ELIZABETH, LLC, PETITIONER
v.
GLADYS MENSING, RESPONDENT

ACTAVIS INC., PETITIONER
v.
JULIE DEMAHY, RESPONDENT

ON WRITS OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE EIGHTH CIRCUIT

BRIEF OF CONSTITUTIONAL ACCOUNTABILITY CENTER AS *AMICUS CURIAE* IN SUPPORT OF RESPONDENTS

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INTEREST OF *AMICUS CURIAE*[1]

Constitutional Accountability Center (CAC) is a think tank, law firm and action center dedicated to fulfilling the progressive promise of our Constitution's text and history. CAC works in our courts, through our government, and with legal scholars to improve understanding of the Constitution and to preserve the rights, freedoms and structural safe-guards guaranteed by our Constitution.

CAC assists state and local officials in upholding valid and democratically enacted measures and historic common law remedies. CAC has filed *amicus* briefs on preemption questions in this Court in *Wyeth v. Levine*, 129 S. Ct. 1187 (2009), and this Term's cases, *Williamson v. Mazda Motor of Am., Inc.*, No. 08-1314 (decided Feb. 23, 2011), and *AT&T v. Concepcion*, No. 09-893 (pending).

CAC seeks to preserve the careful balance of state and federal power established by the Constitution, including its Amendments. CAC thus has a strong interest in this case and the development of preemption law generally.

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[1] The parties' letters of consent to the filing of this brief have been filed with the Clerk. Under Rule 37.6 of the Rules of this Court, *amicus* states no counsel for a party authored this brief in whole or in part, and no counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than *amicus curiae* or its counsel made a monetary contribution to its preparation or submission.

SUMMARY OF ARGUMENT

The Constitution's Supremacy Clause provides for federal law to trump state law when a state law or remedy directly contradicts a valid federal enactment. The text and history of the Clause support federal preemption when a federal law contains language expressly preempting state law or because it would be impossible to comply with both federal law and the state law or remedy. *See generally* Caleb Nelson, *Preemption*, 86 VA. L. REV. 225 (2000).

The Federal Food, Drug and Cosmetic Act (FDCA) does not expressly preempt state-law tort actions, such as the Respondents' suits alleging that they were injured because Petitioners failed to adequately warn that long-term use of their generic drug metoclopromide could cause severe adverse side effects. Accordingly, in order to assert a preemption claim, the Petitioners argue that it would be impossible for them to comply with federal law and satisfy a state-law tort claim suggesting that their generic drug, approved by the Food and Drug Administration (FDA), was inadequately labeled. Petitioners here, like the petitioners in *Wyeth*, have painted the picture that federal labeling requirements necessarily put them between a rock and a hard place when it comes to state failure-to-warn claims. *E.g.*, Pliva Br. 30-46; Actavis Br. 18-26. But the reality is that "a generic pharmaceutical manufacturer, like a brand-name manufacturer, can (and indeed, must) inform FDA of new information about risks that may require a change in the labeling of its drug." U.S. Br. *Amicus*

Curiae 11 (recommending den. of cert.) (hereinafter "U.S. Br. Opp. Cert.").

As the Court explained in *Wyeth v. Levine*, "the manufacturer bears responsibility for the content of its label at all times." 129 S. Ct. 1187, 1197-98 (2009). Explaining this concept further, Justice Thomas noted in concurrence that "[i]nitial approval of a label . . . does not represent a finding [by the FDA] that the drug, as labeled, can never be deemed unsafe by later . . . application of state law." *Id.* at 1210 (Thomas, J., concurring). Because "the FDA's initial approval of a drug is not a guarantee that the drug's label will never need to be changed, . . . nothing in the text of the statutory or regulatory scheme necessarily insulates [drug manufacturers] from liability under state law simply because the FDA has approved a particular label." *Id.* at 1211. As Respondents and the United States have shown, Petitioners' impossibility preemption claim fails on the merits. *See* Resp'ts Br. at 27-46; U.S. Br. Opp. Cert. at 11-22.

Petitioners' remaining claim, touted by their *amici*, is one of implied, "frustration of purposes" or "obstacle" preemption. "Obstacle" preemption, a variant of the Court's implied "conflict preemption" jurisprudence, has occasionally been used to preempt state laws when they frustrate the objectives of a federal enactment. This doctrine, however, has rightfully come under criticism. *See Williamson v. Mazda Motor of Am., Inc.*, 2011 WL 611628 (U.S. S. Ct. Feb. 23, 2011) at *12 (Thomas, J., concurring) (rejecting "purposes-and-objectives pre-emption as inconsistent with the

Constitution"); *Wyeth v. Levine*, 129 S. Ct. 1187, 1211 (2009), (Thomas, J., concurring) (concluding that the "entire body of 'purposes and objectives' pre-emption jurisprudence is inherently flawed"); *Geier v. Am. Honda Motor Co.*, 529 U.S. 861, 907 (2000) (Stevens, J., joined by Souter, Thomas, and Ginsburg, JJ., dissenting) (noting the "potentially boundless (and perhaps inadequately considered) doctrine of implied conflict pre-emption based on frustration of purposes.").

To the extent it is ever appropriate to apply implied obstacle preemption, it is not appropriate here. There is nothing in the statutory text of the Hatch-Waxman Amendments, Pub. L. No. 98-417, 98 Stat. 1585, which encouraged the development of low-cost generic drugs, to suggest that the Amendments were intended to override the FDCA's general preservation of state tort remedies as a complementary form of consumer protection. *See Wyeth*, 129 S. Ct. at 1197, 1199-1200. As this Court noted in *Wyeth*, if Congress wanted to preempt state tort claims based on allegations of inadequate labeling, it could have done so. Given Congress's 1976 enactment of an express-preemption provision for medical devices and its "certain awareness of the prevalence of state tort litigation," Congress "surely would have enacted an express preemption provision" for drug-labeling claims if it believed that all "state-law suits posed an obstacle to its objectives." 129 S. Ct. at 1200.

"[P]re-emption must turn on the text of a federal statute or the regulations it authorizes." *Williamson*, 2011 WL 611628 at *12 (Thomas, J.,

concurring). Neither the FDCA nor the Hatch-Waxman Amendments to the Act authorize preemption of state failure-to-warn actions brought against manufacturers of generic drugs.

ARGUMENT

I. THE CONSTITUTION'S TEXT AND HISTORY SUPPORT IMPLIED PREEMPTION ONLY WHEN A STATE LAW OR REMEDY DIRECTLY CONFLICTS WITH FEDERAL LAW.

Federal law preempts state laws and remedies pursuant to the Constitution's Supremacy Clause. *E.g.*, *Brown v. Hotel & Restaurant Employees & Bartenders Int'l Union Local 54*, 468 U.S. 491, 501 (1984) (explaining that federal preemption occurs "by direct operation of the Supremacy Clause"). The Supremacy Clause "mapped out America's new legal hierarchy," AKHIL REED AMAR, AMERICA'S CONSTITUTION: A BIOGRAPHY 300 (2005), providing:

> This Constitution, and the Laws of the United States which shall be made in Pursuance thereof; and all Treaties made, or which shall be made, under the Authority of the United States, shall be the supreme Law of the Land; and the Judges in every State shall be bound thereby, any Thing in the Constitution or Laws of any State to the Contrary notwithstanding.

U.S. CONST. art. VI, cl. 2.

The text of the Supremacy Clause makes "supreme" the "*Laws* of the United States made in Pursuance [of the Constitution]." U.S. CONST. art. VI, cl. 2 (emphasis added). This ensures that only those provisions that have gone through the "single, finely wrought and exhaustively considered, procedure[s]" specified in the Constitution will be given effect. *INS v. Chadha*, 462 U.S. 919, 951 (1983); U.S. CONST. art. I, § 7.

The Supremacy Clause thus plays a key role in our federalist system, given that the constitutional procedures for making federal law in a bi-cameral, representative legislature are "the principal means chosen by the Framers to ensure the role of the States in the federal system." *Garcia v. San Antonio Metro. Trans. Auth.*, 469 U.S. 528, 550-51 & n.11 (1985) (citing, *inter alia*, Herbert Wechsler, *The Political Safeguards of Federalism: The Role of the States in the Composition and Selection of the National Government*, 54 COLUM. L. REV. 543 (1954)). "[T]he built-in restraints that our system provides through state participation in federal governmental action . . . . ensure that laws that unduly burden the States will not be promulgated." *Id.* at 556. *Accord* THE FEDERALIST No. 62, 408 (James Madison) (B. Wright ed. 1961) (noting that the provision of equal state representation in the Senate in Article I, § 3, represents "a constitutional recognition of the portion of sovereignty remaining in the individual States, and an instrument for preserving that residuary sovereignty").

Broad, implied purposes or general policy reasons are not "[l]aws," which, under Article I, require express agreement among two legislative houses and two democratically-elected branches of government. *See Thompson v. Thompson*, 484 U.S. 174, 191 (1988) (Scalia, J., concurring in the judgment) ("An enactment by implication cannot realistically be regarded as the product of the difficult lawmaking process our Constitution has prescribed."). The Supremacy Clause's textual specification of "Laws of the United States which shall be made in Pursuance [of the Constitution]," U.S. CONST. art. VI, cl. 2, "thus requires that pre-emptive effect be given only to those federal standards and policies that are set forth in, or necessarily follow from, the statutory text that was produced through the constitutionally required bicameral and presentment procedures." *Wyeth*, 129 S. Ct. at 1207 (Thomas, J., concurring), *quoted in Williamson*, at *12 (Thomas, J., concurring).

While the Supremacy Clause affirmed in the text of the Constitution that valid federal law would always trump state law, this strong supremacy rule "comes into play only when courts cannot apply both state law and federal law, but instead must choose between them." Caleb Nelson, *Preemption*, 86 VA. L. REV. 225, 251 (2000). *See also* Viet D. Dinh, *Reassessing the Law of Pre-emption*, 88 GEO. L.J. 2085, 2087-88 (2000) (describing the Supremacy Clause as a "constitutional choice of law rule . . . that gives federal law precedence over conflicting state law"). In this way, state authority is respected and state and local innovation encouraged, while ensuring

that when the federal government duly acts, its enactments become the law of the land.

II. NEITHER THE FDCA NOR THE HATCH-WAXMAN AMENDMENTS AUTHORIZE PREEMPTION OF STATE FAILURE-TO-WARN CLAIMS BROUGHT AGAINST GENERIC DRUG MANUFACTURERS.

As explained in the briefs of Respondents and the United States as *amicus curiae*, the statutory scheme at issue here is the Federal Food, Drug and Cosmetics Act (FDCA), as amended by the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (Hatch-Waxman Amendments). "Congress enacted the FDCA to bolster consumer protection against harmful products." *Wyeth*, 129 S. Ct. at 1199.

In addition to federal health and safety regulation, the States have long played an integral role in protecting consumer safety and promoting public health through state tort law. "[S]tate-law remedies further consumer protection by motivating manufacturers to produce safe and effective drugs and to give adequate warnings." *Id.* at 1200. As this Court re-affirmed in *Wyeth*, when a federal statute touches on "a field which the States have traditionally occupied," the Court "start[s] with the assumption that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress." *Wyeth*, 129 S. Ct. at 1194-95 (quoting *Medtronic, Inc. v.*

Lohr, 518 U.S. 470, 485 (1996), and *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218, 230 (1947) (internal quotations omitted)).

Neither the FDCA nor the Hatch-Waxman Amendments contain language expressly preempting state tort claims related to generic drugs. Certainly, Congress has not hesitated to preempt state-law remedies under the FDCA; for example, Congress passed the Medical Device Amendments of 1976, 21 U.S.C. §360c *et seq.*, which contained an express preemption provision for medical devices. *See Riegel v. Medtronic, Inc.*, 552 U.S. 312 (2008). While "Congress could have applied the pre-emption clause to the entire FDCA," it declined to do so, and "instead wrote a pre-emption clause that applies only to medical devices." *Id.* at 327.

Unlike in the medical-devices context, the statutory and regulatory scheme for generic drugs does not conflict with state-law remedies for inadequate labeling, either expressly or impliedly. This Court has already determined in *Wyeth* that state failure-to-warn claims are not preempted for prescription drugs. There is nothing in the FDCA or the Hatch-Waxman Amendments to support a different conclusion here, despite Petitioners' claims that they have no control over label warnings because generic drug labels must be the same as the relevant brand-name drug label.

While it is true that federal law does require manufacturers of generic drugs to use "labeling . . . [that] is the same as the labeling of the [brand

drug]," 21 C.F.R. 314.94(a)(8)(iii); *see also* U.S. Br. Opp. Cert. at 12-13, it does not absolve them of the responsibility to ensure that their customers are warned of new safety hazards. Quite to the contrary, generic drug manufacturers have a duty to report certain adverse drug experiences to the FDA, 21 C.F.R. § 314.98(a), and annually report "information . . . that might affect the safety, effectiveness, or labeling of the drug product." 21 C.F.R § 314.81(b)(2)(i). Moreover, the FDA has explained that if a generic drug manufacturer "believes that new safety information should be added [to a product's labeling], it should provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised." 57 Fed. Reg. 17,950, 17,961. "[A] generic pharmaceutical manufacturer, like a brand-name manufacturer, can (and indeed, must) inform FDA of new information about risks that may require a change in the labeling of its drug." U.S. Br. Opp. Cert. at 11.[2]

As the Court explained in *Wyeth*, "the manufacturer bears responsibility for the content of its label at all times." 129 S. Ct. at 1197-98. Expanding on this concept, Justice Thomas explained in concurrence that "[i]nitial approval of

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[2] Additionally, generic drug manufacturers may bring relevant information to the attention of the FDA by proposing that the FDA send a "Dear Health Care Professional" letter ("DHCP letter). By working with the FDA in this manner, generic manufacturers may get information out to doctors without going through the labeling process. *Id.*

a label . . . does not represent a finding [by the FDA] that the drug, as labeled, can never be deemed unsafe by later . . . application of state law." *Id.* at 1210 (Thomas, J., concurring). Moreover, because "the FDA's initial approval of a drug is not a guarantee that the drug's label will never need to be changed, . . . nothing in the text of the statutory or regulatory scheme necessarily insulates [drug manufacturers] from liability under state law simply because the FDA has approved a particular label." *Id.* at 1211.

Petitioners and their *amici* argue that, even if it is technically possible for generic drug manufacturers to act under the FDCA as well as a system of state-law liability for inadequate labeling, it would frustrate the purposes of the Hatch-Waxman Amendments. *See* Br. of Pliva, Inc. at 47-61; Br. of Apotex, Inc. as *Amicus Curiae* at 27-29. The main objective of the Amendments, they claim, is to bring low-cost generic drugs to the market quickly; to do this, "Congress specifically intended to free up generic manufacturers from the need to conduct costly research studies and clinical trials required of brand-name manufacturers." Br. of Apotex, Inc. at 28.

This argument exemplifies a basic problem with implied, "frustration of purposes" preemption: "it encourages an overly expansive reading of statutory text." *Wyeth*, 129 S. Ct. at 1215 (Thomas, J., concurring). The search for broad statutory purposes leads to an assumption "that Congress wanted to pursue those policies 'at all costs'—even when the text reflects a different balance." *Id.*

However, as the United States has explained as *amicus curiae*, while Congress undoubtedly intended to speed the availability of low-cost generic drugs, "[t]he Hatch-Waxman Amendments do not pursue the objective of low-cost generic drugs without limitation." U.S. Br. Opp. Cert. at 20. Indeed, "no legislation pursues its purposes at all costs." *Dolan v. United States*, 130 S. Ct. 2533, 2547 (2010) (internal quotation marks omitted). Surely, Congress considered both the need for low-cost generic drugs and the need for *safe* drugs in passing the Hatch-Waxman Amendments—given that the entire purpose of the FDCA is to "bolster consumer protection against harmful products," *Wyeth*, 129 S. Ct. at 1199—and ultimately declined to preempt state-law remedies that may spur adequate product warnings and encourage manufacturers to produce safe and effective drugs.

* * *

In our federalist system of federal powers and retained state authority, it is inevitable that "contests respecting power must arise." *Gibbons v. Ogden*, 22 U.S. (9 Wheat.) 1, 205 (1824). Here, there is no contest: the FDCA, as amended by the Hatch-Waxman Amendments, does not directly conflict with state failure-to-warn actions. To the contrary, "state law offers an additional, and important, layer of consumer protection that complements FDA regulation." *Wyeth*, 129 S. Ct. at 1202. Because the text and history of the Supremacy Clause support displacing state law or remedies only when they actually conflict with

federal law, *amicus* urges the Court to reject Petitioners' preemption arguments.

CONCLUSION

For the foregoing reasons, the decision of the U.S. Court of Appeals for the Eighth Circuit should be affirmed.

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AMICUS CURIAE BRIEF

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ACTAVIS, INC.,

Petitioner,

v.

JULIE DEMAHY,

Respondent.

On Writ of Certiorari to the United States Courts Of Appeals for the Eighth and Fifth Circuits

BRIEF OF TORTS PROFESSORS MARY J. DAVIS, HEIDI LI FELDMAN, THOMAS C. GALLIGAN, JR., MARK P. GERGEN, AND JON HANSON AS *AMICI CURIAE* IN SUPPORT OF RESPONDENTS

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STATEMENT OF INTEREST OF *AMICI CURIAE*[1]

Amici are law professors who regularly teach and write about the law of torts. Each has taught for 20 years or more and each has written extensively in the field. *Amici* have no stake in the outcome of this case other than their academic interest in the logical and rational development of the law. Because this case implicates fundamental tort law issues, *amici* believe that their unique perspective may assist the Court in resolving this case. The Appendix includes further biographical information.

SUMMARY OF ARGUMENT

Petitioners and their *amici* are unduly optimistic about the ability of the Food and Drug Administration ("FDA") to protect the public from unreasonably dangerous drugs. The civil justice system complements FDA regulation of drugs. Even if the agency were adequately funded and staffed, and even if drug-makers always cooperated with the agency to ensure the safety and efficacy of drugs, tort liability would still be necessary to encourage drug-makers to provide adequate warnings about risks that are outside the agency's purview when it approves a drug and

[1] The parties consented to the filing of this brief. No counsel for a party authored this brief in whole or in part and no person other than *amici* and their counsel made a monetary contribution intended to fund its preparation or submission.

labeling. Tort liability also serves compensation and corrective justice interests that FDA regulation was never intended to serve.

Petitioners and their *amici* also have an unduly pessimistic view of the civil justice system. Mechanisms exist within it to protect drug-makers from spurious claims. State courts have struck a balance by adopting rules that shield a drug-maker from design-defect claims while holding a drug-maker liable if it fails to give adequate warning of a drug's risks. This facilitates getting new FDA-approved drugs on the market while using failure-to-warn liability to encourage dissemination of risk information and so enable health-care professionals and the public to make informed decisions about drugs. Other rules address specific arguments for preemption. Rules of evidence enable courts to screen out claims that lack a sound scientific basis. The hypothetical danger of drug-makers' inundating the public with warnings to avoid liability is dealt with by the learned intermediary doctrine, which enables drug-makers to satisfy the duty to warn by providing information to health-care professionals.

The American Law Institute ("ALI"), state courts, and state legislatures have grappled with arguments for and against requiring courts and juries to defer to FDA approval of a drug's labeling in developing the "regulatory compliance" defense. Many state statutes require some deference to FDA approval of a drug's labeling. Those rules would not shield petitioner here because the FDA never approved the long-term use of

metoclopramide. When the FDA did consider the risks of long-term use, moreover, it mandated that a much stronger boxed warning be added to the label.

This experience teaches that preemption is not an either-or proposition. A narrow rule of preemption is similar to a strong form of the common-law defense of regulatory compliance. This would make FDA approval of a warning regarding specific risk determinative of the reasonableness of the warning for that risk if the FDA considered all relevant information. A broad rule would make the FDA solely responsible for ensuring the adequacy of warnings of FDA-approved drugs by precluding all failure-to-warn claims regarding FDA-approved drugs. This would shield a drug-maker from liability even if it withheld relevant risk information from the FDA or otherwise failed to cooperate, and even with respect to risks that appear post-marketing or that involve "off-label" uses, which the FDA has no opportunity to consider. This would be a radical change from the status quo. This Court should leave it to Congress to tailor an appropriate preemption rule and to decide whether the rule should apply retroactively.

Respondents each brought a typical state-law failure-to-warn case. The elements of such a case are well-established in Louisiana, Minnesota, and nationwide. Pliva's effort to impose an additional obligation on respondents – to prove what the FDA would have done if petitioners had fulfilled their obligations to recommend adequate warnings – is unpersuasive. It misconceives the elements of a failure-to-warn

case, misconstrues this Court's decision in *Wyeth v. Levine*, 129 S. Ct. 1187 (2009), and misconceives the nature of the causation inquiry. Respondents need not disprove petitioners' affirmative defenses as part of their affirmative cases.

ARGUMENT

I. Preemption of state-law tort claims based on FDA regulation of a generic drug is unwarranted because the civil justice system complements the FDA's regulation of drugs

The civil justice system complements FDA regulation of generic drugs on two general dimensions. First, tort liability serves several important functions that FDA regulation of drugs – either brand-name or generic – was never intended to serve. Most of those functions involve compensating people who are injured, usually because a drug-maker failed to provide adequate warning of a drug's risks. Whether the civil justice system should be preempted from serving those compensatory functions raises fundamental questions of morality and policy. Second, tort liability complements the FDA's regulatory function. Whether the civil justice system should be preempted from serving that function turns on an assessment of the relative strengths of FDA regulation and civil liability as mechanisms for protecting people from unreasonably dangerous drugs.

Ultimately, both answers turn on whether society chooses to err on the side of over- or under-protecting the public from unreasonably dangerous drugs. State courts have struck a balance by eliminating barriers to the introduction of new drugs, relying on the FDA to keep unreasonably dangerous drugs off the market, while imposing failure-to-warn liability to encourage dissemination of risk information and thus enable health-care professionals and the public to make informed judgments about drugs.

Neither the FDA itself (with one since discredited[2] exception) nor any other official body has ever concluded that a general rule preempting failure-to-warn liability is needed to enable the agency to accomplish its mission with respect to either brand-name or generic drugs.[3]

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[1] In the preamble to a 2006 FDA regulation governing the content and format of prescription drug labels, the FDA – in a reversal of previous policy – declared that "FDA approval of labeling . . . preempts conflicting or contrary State law." 71 FED. REG. at 3935. Two years ago, this Court resoundingly rejected the FDA's attempt to preempt state law through its 2006 preamble. See *Wyeth v. Levine*, 129 S. Ct. 1187, 1200-04 (2009). It did "not merit deference," *id.* at 1201; its adoption was procedurally questionable, *id.*; and it was "at odds with what evidence we have of Congress' purposes," *id.*

[2] The 2000 proposed regulations on prescription drug labeling recognized this explicitly. The preamble stated: "FDA has determined that this proposed rule does not contain policies that have federalism implications or that preempt State law." 65 FED. REG. 81,082, 81,103 (Dec. 22, 2000).

A. The civil justice system serves compensation and loss-spreading functions outside the scope of FDA regulation

By compensating individuals harmed by drugs, tort law serves some ends that FDA regulation simply is not meant to serve. Most importantly, "preemption completely eliminates the corrective justice role that common law courts have played in this country since its founding." THOMAS O. MCGARITY, THE PREEMPTION WAR 33 (Yale 2008). For much of this country's history, the purpose of tort law was thought to be redressing moral wrongs, not regulation or deterrence. In the last half-century, it has come to be understood as also serving a regulatory function. But corrective justice or compensation remain important. See *Warriner v. Stanton*, 475 F.3d 497, 501 (3d Cir. 2007) (reaffirming that New Jersey's tort policies consist primarily of compensation and deterrence); *Hannah v. Heeter*, 584 S.E.2d 560, 566 (W. Va. 2003) ("the three fundamentals of tort law are morality, compensation, and deterrence") (internal quotation marks omitted). See generally Gary T. Schwartz, *Mixed Theories of Tort Law: Affirming Both Deterrence and Corrective Justice*, 75 TEX. L. REV. 1801 (1997). In Europe, civil liability generally is still understood to serve corrective justice. For this reason, there has been almost no movement in Europe to eliminate civil liability for

unreasonably dangerous products and to rely solely on administrative regulation of dangerous products.[4]

From the perspective of corrective justice, FDA approval of drug labeling is relevant only insofar as it establishes that a drug-maker is not morally blameworthy in failing to provide an additional warning. FDA approval of a label would be significant if the FDA advised a drug-maker that a particular warning was adequate regarding a specific risk. It would be decisive if the FDA forbade the drug-maker from providing an additional warning. Of course, neither of those is relevant in the present cases. Outside of those two situations, FDA approval is of no obvious relevance.

Compensation through strict liability also spreads losses. See, e.g., *New Texas Auto Auction Servs., LP v. Gomez De Hernandez*, 249 S.W.3d 400, 404 (Tex. 2008) (stating justifications for strict liability as "(1)

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[4] The European Union ("EU") generally has two tiers of administrative approval, at the EU level and the member-state level. See CHRISTOPHER HODGES, EUROPEAN REGULATION OF CONSUMER PRODUCT SAFETY, Ch. 4 (Oxford 2004). An industry position paper has cited "a very low level of compensation claims" as evidence of the success of the administrative system. *Id.* at 43. The 1985 European Directive on Product Liability § 4(1)(a) makes compliance with a regulation a defense. See SIMON WHITTAKER, LIABILITY FOR PRODUCTS 522 (Oxford 2005) ("This defence is not, of course, a defence of compliance with public standards (though such a defence has been suggested): it requires that the defect itself results from the regulatory standard.").

compensating injured consumers, (2) spreading potential losses, and (3) deterring future injuries"); *Antone v. Greater Arizona Auto Auction*, 155 P.3d 1074, 1076 (Ariz. Ct. App. 2007) ("[T]he underlying justification for imposing strict liability is risk/cost spreading to those parties in the distribution chain that are best able to both bear the cost and protect the consumer from defective products."), *review denied* (Ariz. Sept. 25, 2007). The loss-spreading justification is buttressed by the law and economics insight that the cost of accidents is minimized by imposing costs on "the 'cheapest cost avoider' or [the actor] who is in the best position to make the cost-benefit analysis between accident costs and accident avoidance costs and to act on that decision once it is made." *Beshada v. Johns-Manville Prods. Corp.*, 447 A.2d 539, 548 (N.J. 1982) (citing Guido Calabresi & Jon T. Hirschoff, *Toward a Test for Strict Liability in Torts*, 81 YALE L.J. 1055 (1972)). See generally Robert L. Rabin, *Reassessing Regulatory Compliance*, 88 GEO. L.J. 2049, 2071 (2000).

For a court or state legislature that held those views, an FDA cost-benefit determination would be irrelevant, even when the lawmaker is confident the FDA is right. *Schneider Nat'l, Inc. v. Holland Hitch Co.*, 843 P.2d 561, 580 (Wyo. 1992) ("The risk allocation concept means that strict liability is not based on 'fault.' Instead of considering each actor's negligence or fault, the person most able to avoid accidents . . . is held liable for the cost of the accident.") (citations omitted). The court or legislature would still want to

impose liability to spread losses resulting from risks that were worth taking.[5] Cf. *Bruesewitz v. Wyeth LLC*, No. 09-152, slip op. 3-5 (U.S. Feb. 22, 2011) (describing compensation system to spread losses resulting from vaccine risks). If the court or legislature thought there was a risk of regulatory error, then they would have an additional reason for imposing strict liability for it would increase their confidence that a company would warn of a risk if the benefits of the additional warning outweighed the cost.

The U.S. trend in products liability law has been away from strict liability and towards negligence-based liability, particularly for pharmaceutical design defects.[6] See Jane Stapleton, *Liability for Drugs in*

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[5] See *Wilson v. Piper Aircraft Corp.*, 577 P.2d 1322, 1333 (Or. 1978) (Linde, J., concurring) ("In a state where common law or legislation imposed absolute liability on a producer for certain kinds of harm in fact caused by his product, the fact that it had been thoroughly tested and approved for safety would be immaterial. But when liability is predicated on finding a design 'dangerously defective,' not 'duly safe,' or short of some similarly phrased standard of safety, then a careful comparison of that standard and the one attested to by the certificate becomes important.").

[6] *Grundberg v. Upjohn Co.*, 813 P.2d 89 (Utah 1991), cites FDA regulation and the "unavoidably unsafe" nature of drugs as reasons not to impose strict liability. *Id.* at 90-92. This leaves to "courts to find liability under circumstances of inadequate warning, mismanufacture, improper marketing, or misinforming the FDA – avenues for which courts are better suited." *Id.* at 99.

the U.S. and EU: Rhetoric and Reality, 26 REV. LITIG. 991 (2007).[7] But, as Professor Rabin has observed:

> More than a half century after *Escola* [*v. Coca Cola Bottling Co.*, 150 P.2d 436 (Cal. 1944)], the courts still have not reached a consensus on which rationale [compensation or regulation] should prevail. The divide is defined by those courts (and commentators) that would limit design defect and inadequate warning liability to some version of risk-benefit analysis, contrasted with those that would recognize a consumer expectations rationale, as well.

Rabin, 88 GEO. L.J. at 2071.

In particular, while it is now a minority position, some courts apply the "hindsight test" to determine whether a product was defective or, in the case of an FDA-approved drug, whether there was inadequate

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[7] The gist of Professor Stapleton's argument is that the Europeans should learn from the U.S. experience and move away from a view that, at least rhetorically, treats liability for defective products, including drugs, as being strict. The leading European case on the character of liability is *A v. National Blood Authority*, [2001] 3 All ER 289 (Q.B.). It involves claims by Hemophiliacs given transfusions of blood infected by Hepatitis C. The court held the defendant liable, although the defendant was not negligent in failing to screen against Hepatitis C given the state of the art when the claims arose. The court interpreted the Product Liability Directive as intended to "achieve a higher and consistent level of consumer protection throughout the Community and render recovery of compensation easier, and uncomplicated by the need for proof of negligence." *Id.* at 310-11.

warning. The "hindsight test" assesses whether a product was defective – or, in the case of an FDA-approved drug, whether a warning was adequate – taking account of information that arose after a product was marketed. See *Sternhagen v. Dow Co.*, 935 P.2d 1139, 1147 (Mont. 1997); DAVID G. OWEN, PRODUCTS LIABILITY LAW § 8.7 (2005). A court that applies the hindsight test will hold a drug-maker liable if risks that became apparent only in hindsight warranted an additional warning. The court would not second-guess the FDA's decision not to require a warning for the agency does not have the benefit of hindsight.

Congress could decide that the interest in compensation is insufficient to justify maintaining failure-to-warn liability as a complement to FDA regulation. Congress has not done so here. On the contrary, post-Vioxx legislation expressly ratifies a regulatory requirement that drug-makers warn the public of risks of which they are aware without waiting for FDA action.[8] This requirement is a linchpin of civil liability because it demonstrates that FDA-approved warnings are not a ceiling on a drug-maker's duty to warn.

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[8] See Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 901(a), 121 Stat. 823, 925-26 (codified at 21 U.S.C. § 355(o)(4)(I)) ("2007 FDA Amendments Act").

B. The civil justice system regulates decisions and activities outside the purview of the FDA's approval of a drug and its labeling

Tort liability also has regulatory value. Sometimes it is a safeguard against regulatory failure. The FDA sometimes fails to protect the public from unreasonably dangerous drugs. The Vioxx experience is instructive:

> The picture that the Vioxx experience paints of FDA regulation of pharmaceutical products is one of an agency that has been very accommodating to the regulated industry in approving new and potentially highly beneficial drugs but not especially adept at detecting adverse side effects once these drugs are in use. At the same time, the pharmaceutical industry has been very aggressive in pushing potential "blockbuster" drugs through the approval process, and it has not been particularly forthcoming with the agency and the public when it comes upon warning signs of potential adverse outcomes. . . . Dr. David J. Graham . . . called the Vioxx episode "a profound regulatory failure," and he pessimistically concluded that "FDA as currently configured is incapable of protecting America against another Vioxx."

McGARITY, *supra* at 16.

Regulatory failure has many causes, some of which this Court recognized in *Wyeth v. Levine*, 129 S. Ct. 1187, 1202 & nn.11-12 (2009). The FDA is

inadequately funded and staffed, it may be subject to regulatory capture, drug-makers may withhold relevant information, and they may resist FDA action. But even if the agency were adequately funded and staffed, and drug-makers always worked hand-in-hand with the agency to ensure the safety and efficacy of drugs, failure-to-warn liability would still be warranted to encourage drug-makers to warn about risks that are outside the purview of the FDA's decision when it approves a new drug and its labeling. For this reason, state courts and legislatures generally agree that regulatory approval of conduct should shield an actor from liability only regarding risks that were considered in approving the conduct. These reasons for maintaining failure-to-warn liability are independent of the quality of the FDA's analysis in approving a drug and its labeling.

1. The civil justice system creates the incentive system by which post-marketing risk information comes to light

Approval of a new drug is typically based on limited clinical studies involving relatively small populations and relatively short time periods. "Once the drug enters the marketplace, risks that are relatively rare, that manifest themselves only after an extended period of time, or that affect vulnerable subpopulations, begin to emerge. These are often not risks foreseen by the drug's manufacturer or the FDA and, for that reason, are not addressed on the label."

David A. Kessler & David C. Vladeck, *A Critical Examination of the FDA's Efforts to Preempt Failure-to-Warn Claims*, 96 GEO. L.J. 461, 466 (2008) (footnote omitted). "[F]ully one-half the adverse effects of newly marketed drugs are not discovered until after the drugs have been on the market for a while." MCGARITY, *supra* at 237-38.

Historically, the FDA has expended vastly more resources evaluating new-drug applications than monitoring adverse events for existing drugs. See Kessler & Vladeck, 96 GEO. L.J. at 485. Doctor Kessler and Professor Vladeck describe new tools and resources given to the FDA by the 2007 FDA Amendments Act to strengthen the agency's post-approval surveillance. *Id.* at 487-90.[9] But they conclude "it remains to be seen whether this increased surveillance will help the agency to recognize emerging safety problems more quickly." *Id.* at 490. Some problems are endemic. It is difficult for the FDA to assess adverse reaction reports when it "does not know how many people are using the drug or have information about their conditions." *Id.* And it takes time for the FDA to take effective action, particularly if its information is inconclusive and a drug-maker resists.[10]

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[9] These include express statutory authority to update labeling and to order new clinical trials, something the FDA had done in the past depending on the cooperation of drug-makers.

[10] An FDA advisory panel recommended in early 2001 that the Vioxx label warn about the cardiovascular risk. This

(Continued on following page)

While concerns with post-marketing risk information are relevant for all drugs, the issue is particularly important for generic drugs. By definition, generic drugs are those that have been available in the marketplace for years, and are thus drugs for which post-marketing risk information is more likely to be significant.

2. The civil justice system regulates "off-label uses" that largely fall outside the scope of FDA regulation

Drugs often are prescribed for "off-label use," meaning a use not approved by the FDA. It is estimated that "40-60% of prescriptions were written for off-label uses" and that "50% of cancer treatment drugs, 80-90% of drugs used to treat rare diseases, and 80% of drugs used in the pediatric field are prescribed off-label to patients." James O'Reilly & Amy Dalal, *Off-Label or Out of Bounds? Prescriber and Marketer Liability for Unapproved Uses of FDA-Approved Drugs*, 12 ANNALS HEALTH L. 295, 298 (2003). The contentious issue regarding FDA

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recommendation was based on a study that showed a correlation but Merck argued there was another cause. "Merck vigorously resisted this suggestion, arguing that the gastrointestinal benefits of Vioxx outweighed any cardiovascular risk. After fourteen months of negotiations, Merck and the agency compromised" on a diluted warning. The FDA acted quickly to take Vioxx off the market once it received the results of a more conclusive study in September 2004. See MCGARITY, *supra* at 7-8.

regulation of off-label uses has been whether and to what extent drug-makers may promote off-label uses or educate physicians and the public about off-label uses. The FDA can warn about an unreasonably risky off-label use, and can ask a drug-maker to stop marketing a drug when it learns of unreasonably dangerous off-label uses. But this occurs after the fact, sometimes tragically so.

Fen-Phen is a case in point. Fenfluramine was combined with Phentermine to create a dietary suppressant that did not induce asleep. The popular press reported 1992 study results that found Fen-Phen users lost 30 pounds on average in 9 months. It was off to the races. By 1996, physicians had written over 5 million Fen-Phen prescriptions. The FDA never approved the combination. By the time the FDA asked Wyeth in 1997 to stop marketing Fen-Phen and a sister drug, Redux, an estimated 45,000 women had already been harmed. See Sue McGrath, *Only a Matter of Time: Lessons Unlearned at the Food and Drug Administration Keep Americans at Risk*, 60 FOOD & DRUG L.J. 603, 613-16 (2005); ALICIA MUNDY, DISPENSING WITH THE TRUTH (St. Martin's 2001).

Because Reglan and metoclopramide were approved only for short-term use, these cases involve an "off-label use" of a drug – indeed, a common "off-label use" that was well-known to the drug-makers.

3. The civil justice system regulates unexamined risks that the FDA never considered

Petitioners and their supporting *amici* argue that respondents' failure-to-warn claims should be preempted based on the FDA's approval of Reglan's short-term use years before. Ultimately, the FDA examined the risks of long-term use of metoclopramide and in 2009 finally required a "Boxed Warning." See Resp. Br. 10-11 (describing warning). That action, of course, occurred several years after the events at issue here.

There is no suggestion that the FDA considered the risks of long-term usage when it approved Reglan. Indeed, its approval of the drug only for short-term use is clear evidence that it did not. There is accordingly no more reason to find preemption here on the basis of the FDA's approval of Reglan than there was to find preemption in *Wyeth v. Levine*, 129 S. Ct. 1187 (2009), when this Court refused to find preemption based on the FDA-approved labeling of Phenergan when the FDA had not considered the risks of IV-push administration of the drug.

II. Preemption of state-law tort claims based on FDA regulation of a drug is unnecessary because the civil justice system defers to FDA expertise and protects drugmakers from spurious claims

Petitioners and their supporting *amici* seek to portray a range of terrible consequences if generic

drug-makers are held responsible under state tort law for their failures. Not surprisingly, in the real world – where state-law failure-to-warn claims have long been available – those consequences have not materialized. State courts and legislatures recognize the need for an appropriate balance. They recognize the great good that drugs can do but also the accompanying risks. And they respect the FDA's expertise in regulating drugs and deciding which risks merit warnings. But they have steadfastly refused to grant total immunity to drug-makers from failure-to-warn liability in the absence of an FDA decision that the specific risk in question did not warrant warning. Only one state legislature, Michigan, has taken that step. Petitioners ask this Court to do something that neither Congress, nor any other state legislature, nor any state court has thought prudent.

A. Tort law already defers to FDA's expertise in drug approval

Over the last half century, tort law has evolved to a position in which courts largely cede to the FDA the authority to decide whether a new drug should be allowed on the market. Drug-makers face a risk of liability only for failing to warn of a drug's risks. Professor Owen summarizes the story:

> Whether and how prescription drugs in particular should be treated differently from other types of products has consumed more time and effort, and resulted in the gnashing of more teeth, than about any other

> particular issue in all of products liability law. In addition to featuring two prominent Restatement provisions – comment k to § 402A of the Restatement (Second) of Torts and § 6(c) of the Third Restatement, the drug design defect story wends through two of the most prominent cases in products liability law history – *Feldman v. Lederle Laboratories* and *Brown v. Superior Court*. The issue is complex, involving the learned intermediary doctrine, product category liability, state of the art, the battle for supremacy between the consumer expectations and risk utility tests of liability for design defectiveness, the never-ending struggle between negligence and strict liability, how design and warning defect notions fit together, federal preemption, and, at bottom, whether drugs in fact are different from other types of products, and whether they should be treated differently by products liability law.

OWEN, *supra* at 549.

Professor Owen refers to an ongoing debate over when and how FDA-approved drugs should be shielded from products liability claims in general and design-defect claims in particular. The issue emerges only after true strict liability (sometimes referred to as absolute liability) is rejected in favor of negligence-based liability. Once this choice has been made, drugs are the paradigmatic example of what has come to be called an "unavoidably dangerous" product. This is a product – like a cigarette, a gun, or a knife – that must be dangerous if it is to perform its intended

function. Products liability law generally is open to a claim that an unavoidably dangerous product should be designed more safely so it could serve its intended function with reduced risk.

Commentators debate whether the law should permit a claim that a product was so dangerous, and of so little utility, that it is wrong to sell the product even if it can be made no safer while performing its intended function. While that is hotly contested, there is a consensus that FDA-approved drugs should be shielded from both types of claims. The FDA, better than a judge or jury, can decide whether the benefits of a new drug sufficiently outweigh the risk to justify placing the drug on the market, and whether the design of a drug can be tweaked to realize the benefits with reduced risk.

The debate has been over precisely when and how an FDA-approved drug should be shielded from a design-defect claim. Cf. *Bruesewitz*, *supra*. Some courts adopted a categorical rule precluding design-defect claims for FDA-approved drugs. That approach was taken in *Brown v. Superior Court*, 751 P.2d 470 (Cal. 1988), and adopted in cases such as *Grundberg v. Upjohn Co.*, *supra*.[11] Others took a case-by-case

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[11] The *Grundberg* court summarized the justification:

> We find this extensive regulatory scheme capable of and appropriate for making the preliminary determination regarding whether a prescription drug's benefits outweigh its risks. The structured follow-up program imposed by law ensures that drugs are not

(Continued on following page)

approach under which the judge makes a preliminary determination whether a drug was defective as marketed or as designed. This is the approach taken in *Feldman v. Lederle Laboratories*, 479 A.2d 374 (N.J. 1984), and adopted and amplified in cases such as *Freeman v. Hoffman-La Roche, Inc.*, 618 N.W.2d 827 (Neb. 2000). This takes the issue out of the hands of the jury. The Restatement (Third) of Torts: Products Liability § 6(c) (1998) straddles the two approaches by allowing a claimant to proceed with a design-defect claim only if the foreseeable risks are so great, and foreseeable benefits so small, that no health-care professional would prescribe the drug "for any class of patients." This "leaves a very small window for design defect claims for prescription drugs, a window so tiny that almost no drug claim could fit through it." OWEN, *supra* at 557.

The upshot is that courts generally have ceded to the FDA the power to determine whether a new drug should be placed on the market as designed, so long as the drug-maker is not aware of risks that it fails to disclose to the FDA. While ceding this ground, courts have retained failure-to-warn liability. Thus, the

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placed on the market without continued monitoring for adverse consequences that would render the FDA's initial risk/benefit analysis invalid. Allowing individual courts and/or juries to continually reevaluate a drug's risks and benefits ignores the processes of this expert regulatory body and the other avenues of recovery available to plaintiffs.

813 P.2d at 97.

Utah Supreme Court observed in *Grundberg*, 813 P.2d at 99: "Relying on the FDA's screening and surveillance standards enables courts to find liability under circumstances of inadequate warning, mismanufacture, improper marketing, or misinforming the FDA – avenues for which courts are better suited." This compromise facilitates getting new drugs to market while using failure-to-warn liability to encourage dissemination of information about risks to enable health-care professionals and the public to make informed decisions about drugs.

B. This Court's decision in *Daubert* and the "learned intermediary doctrine" protect defendants from unjustified liability

Other judicially developed doctrines address specific policy arguments for preemption. One argument raises the specter of unsophisticated juries overriding the FDA based on junk science. Eighteen years ago, this Court, in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), interpreted Federal Rules of Evidence 702 to empower trial judges to screen proffered expert scientific testimony to ensure that the testimony meets basic standards of scientific validity and reliability. Professor Owen observes: "Post-Daubert, the federal district courts, exercising their newly appointed 'gatekeeper' function, have scrutinized expert testimony more closely, often holding rigorous pre-trial 'Daubert hearings' – that are often outcome determinative – to determine

the admissibility of proffered expert testimony." David G. Owen, *A Decade of Daubert*, 80 DENV. U. L. REV. 345, 362 (2002). While counts vary, it is estimated that a majority of states now apply a similar standard. See OWEN, *supra* at 376.

Another argument raises the specter of drug-makers responding to the risk of liability by overwhelming consumers with warnings. This is avoided by the "learned intermediary" doctrine, which shields makers of prescription drugs from claims for failure to warn the public.[12] One codification of the doctrine states:

> [A prescription] drug is not defective due to inadequate warning or instruction if its manufacturer provides otherwise adequate warning and instruction to the physician or other legally authorized person who prescribes or dispenses that [prescription] drug for a claimant in question and if the federal food and drug administration has not provided that warning or instruction relative to that [prescription] drug is to be given directly to the ultimate user of it.

Ohio Rev. Code Ann. § 2307.76(C).

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[12] "The doctrine was first recognized in case law over 50 years ago, and since that time has been recognized and applied in nearly all jurisdictions in the country." Richard B. Goetz & Karen R. Growdon, *A Defense of the Learned Intermediary Doctrine*, 63 FOOD & DRUG L.J. 421, 421 (2008).

C. The regulatory compliance defense protects defendants from unjustified liability

The American Law Institute (ALI), state courts, and state legislatures have grappled with whether and when civil courts and juries should defer to regulatory approval of allegedly negligent conduct in considering what has come to be called the regulatory compliance defense. A broad consensus holds that regulatory approval of conduct should shield an actor from negligence liability only if the regulator considered the specific risk in question when it approved the conduct.

1. The evolving ALI views

Over the last generation, the ALI has slowly moved towards a position that treats regulatory approval of allegedly negligent conduct as a basis for taking the issue of negligence away from the jury if the regulator considered the specific risk in question and decided that additional precautions were not worth taking.

While stating the traditional common-law position that statutes and regulations set a floor and not a ceiling on what is reasonable conduct, Restatement (Second) of Torts § 288C (1965) briefly acknowledges in Comment *a* the possibility that a court may treat a statute or regulation as determinative of what is reasonable conduct:

> [A] legislative or administrative minimum does not prevent a finding that a reasonable man would have taken additional precautions where the situation is such as to call for them. . . . Where there are no such special circumstances, the minimum standard prescribed by the legislation or regulation may be accepted by the triers of fact, or by the court as a matter of law, as sufficient for the occasion. . . .

More recent Restatements expand on when a court may take the issue of the unreasonableness of conduct or the defectiveness of a product away from the jury because of legislative or regulatory approval of the conduct or product. Restatement (Third) of Torts: Products Liability § 4 (1998) explains in Comment *e*:

> Occasionally, after reviewing relevant circumstances, a court may properly conclude that a particular product safety standard set by statute or regulation adequately serves the objectives of tort law and therefore that the product that complies with the standard is not defective as a matter of law. Such a conclusion may be appropriate when the safety statute or regulation was promulgated recently, thus supplying currency to the standard therein established; when the specific standard addresses the very issue of product design or warning presented in the case before the court; and when the court is confident that the deliberative process by which the safety standard was established

> was full, fair, and thorough and reflected substantial expertise. Conversely, when the deliberative process that led to the safety standard with which the defendant's product complies was tainted by the supplying of false information to, or the withholding of necessary and valid information from, the agency that promulgated the standard or certified or approved the product, compliance with regulation is entitled to little or no weight.

Restatement (Third) of Torts: Liability for Physical and Emotional Harm § 16 (2005), after canvassing the situations in which compliance is not a defense, explains in Comment *f* when compliance may be a defense:

> *Statutory compliance as a limitation on liability.* While the Comments above explain the rule to the effect that compliance with statutes is usually no more than evidence of nonnegligence, the observations in the Comments suggest the rule's own limits. When the statute directly addresses the particular safety problem before the court, when the statutory scheme evidently seeks to identify all the precautions called for by the general negligence standards in § 3, and when the particular case involves no unusual circumstances, the court may conclude that the actor's compliance with the statute shows that the actor's conduct does not lack reasonable care. In reaching this conclusion, the court can take into account several factors,

> including the evident thoroughness of the statute and the desirability of a uniform liability standard that can simplify litigation and provide parties with appropriate guidance as to what precautions are expected of them.

ALI's Reporters' Study, *Enterprise Responsibility for Personal Injury* (1991), goes furthest towards endorsing a strong defense of regulatory compliance. After stating that, at a minimum, regulatory compliance should create a presumption of non-negligence and should shield an actor from punitive damages, the study goes on to recommend "making regulatory compliance a complete bar to tort liability once certain carefully-defined conditions have been satisfied respecting the regulation." *Id.* at 110. One condition is that "[t]he agency must have addressed the specific risk at issue in the case at hand, and must have made an explicit judgment about what type of legal controls are appropriate." *Id.* That condition is not satisfied here because the FDA never addressed the specific risk of long-term use of Reglan or metoclopramide.

2. The regulatory compliance defense in the courts

Courts endorsing a regulatory compliance defense limit it to cases in which the regulator considered the specific risk at issue when approving the challenged conduct. Justice Linde expressed the requirement pithily in a concurring opinion in *Wilson v. Piper Aircraft*, 577 P.2d at 1334-35:

> [I]t should be defendant's burden to show that a governmental agency has undertaken the responsibility of making substantially the same judgment that the court would otherwise be called on to make; and if so, it should then be plaintiff's burden to show that the responsible agency has not in fact made that judgment with respect to the particular "defect" at issue.

One leading case, *Ramirez v. Plough, Inc.*, 863 P.2d 167 (Cal. 1993), involved a challenge to the labeling of a non-prescription drug. The plaintiff claimed it was negligent to market children's aspirin in California without a warning in Spanish of the risk of Reye's Syndrome. The California Supreme Court, affirming summary judgment for the defendant, found the FDA's decision not to require a Spanish-language warning conclusive on the issue of negligence: "[T]he FDA has concluded that despite the obvious advantages of multilingual package warnings, the associated problems and costs are such that at present warnings should be mandated only in English." *Id.* at 175.[13] In other words, court ruled for the defendant only because it concluded that the FDA

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[13] The bases for this conclusion were that the FDA required Spanish-language warnings on medicine sold in Puerto Rico and other territories where the predominant language was Spanish, 863 P.2d at 174, and the FDA had experimented with foreign-language package inserts but concluded that the cost outweighed the benefits, *id.* at 175.

had considered the relevant cost and benefits and decided the cost outweighed the benefits.

3. State legislation

State legislatures have moved cautiously in making regulatory approval of conduct or a product a defense to a claim that the conduct was unreasonable or the product was defective. Regulatory approval of conduct or a product is generally relevant under state statutes only if the regulator specifically addressed the risk at issue in a case, and the approval creates only a presumption of non-negligence and non-defectiveness. Only Michigan has enacted a statute that shields a drug-maker from liability for failure to warn about risks that the FDA did not consider in approving a drug and its labeling. Some states have enacted statutes that make FDA approval of a drug and labeling a general shield to liability for punitive damages, even with regards to risks not considered by the FDA.

Presumption of non-negligence and non-defectiveness. A significant number of states have enacted statutes that provide for a rebuttable presumption of non-negligence and non-defectiveness if a regulator approves of conduct or a product. Some of the statutes are general while some apply only to FDA-approved drugs and labeling. See Ark. Code Ann. § 16-116-105; Colo. Rev. Stat. § 13-21-403; Fla. Stat. § 768.1256(1); Ind. Code § 34-20-5-1; Kan. Stat. Ann. § 60-3304(a) (enacting Model Uniform Product

Liability Act § 108(A)[14] verbatim); Mich. Comp. Laws § 600.2946(4); N.J. Stat. Ann. § 2A:58C-4 (warning or instruction in compliance with regulatory approval under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act); N.D. Cent. Code § 28-01.3-09; Tenn. Code Ann. § 29-28-104; Tex. Civ. Prac. & Rem. Code Ann. § 82.007.[15]

The rebuttable presumption is not toothless. *Schultz v. Ford Motor Co.*, 857 N.E.2d 977 (Ind. 2006), holds that the jury is told of the presumption. That invites the jury to defer to an agency if it is uncertain about whether a product was unreasonably dangerous. One court went further and endorsed instructing the jury that regulatory compliance is "strong and substantial evidence" of non-negligence and non-defectiveness. *Lorenz v. Celotex Corp.*, 896 F.2d 148, 149 (5th Cir. 1990) (Texas law).

Louisiana and Minnesota have not enacted such legislation. Even if one had, however, the presumption would not have applied in either of these cases because the FDA did not approve Reglan or metoclopramide for the long-term use on which respondents' claims are based. The presumption applies only if "the specific injury causing aspect of the product

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[14] The Model Uniform Product Liability Act was published by the Department of Commerce in 1979. See 44 FED. REG. 62,714 (Oct. 31, 1979).

[15] Wash. Rev. Code § 7.72.050(1) merely provides that the trier of fact may consider evidence of compliance. This was to reverse a Washington case holding that the evidence was not admissible.

conformed to or was in compliance with the legislative or administrative regulatory standard." *Alvarado v. J.C. Penney Co.*, 735 F. Supp. 371, 373 (D. Kan. 1990) (quoting comments to Model Uniform Product Liability Act § 108). See also *Ehlis v. Shire Richwood, Inc.*, 233 F. Supp. 2d 1189, 1198-99 (D.N.D. 2002) (holding the presumption does not apply to an "off-label" use because the use was not approved by the FDA), *aff'd*, 367 F.3d 1013 (8th Cir. 2004).

A shield against punitive damages. Several states statutorily shield drug-makers from punitive damages if a drug is manufactured and labeled in accordance with FDA approval. See Ariz. Rev. Stat. § 12-701; N.J. Stat. Ann. § 2A:58C-5(c); N.D. Cent. Code § 19-02.1-26(1); Ohio Rev. Code Ann. § 2307.80(C); Or. Rev. Stat. § 30.927; Utah Code Ann. § 78B-8-203. Typically, the shield is removed if a manufacturer knowingly withholds relevant information from the FDA. Unlike the presumption, these statutes do not require that the FDA have considered the specific risk at issue. See, e.g., Ariz. Rev. Stat. § 12-701.

The Michigan statute. In 1995, Michigan enacted a statute providing

> a drug is not defective or unreasonably dangerous, and the manufacturer or seller is not liable, if the drug was approved for safety and efficacy by the United States food and drug administration, and the drug and its labeling were in compliance with the United States food and drug administration's

> approval at the time the drug left the control of the manufacturer or seller.

Mich. Comp. Laws § 600.2946(5). The statute was upheld in *Taylor v. SmithKline Beecham Corp.*, 658 N.W.2d 127 (Mich. 2003).

The statute is unique in its breadth. It shields a drug-maker from any liability based on a theory of negligence or products liability if the FDA approved the drug. Unlike the regulatory compliance defense and the rebuttable presumption statutes, the defense is not limited to claims involving risks actually addressed by the FDA. There is no exception for risks that appear post-marketing. And there is no exception for "off-label" uses the FDA never approved. The only exceptions in the statute are if (i) a company intentionally withholds information that it is required to submit under federal law that would have led the FDA not to approve the drug, or to withdraw approval, and (ii) an FDA official is bribed. Mich. Comp. Laws § 600.2946(5)(a)-(b).

III. This Court should leave it to Congress to craft appropriate preemption rules

Preemption is not a simple either-or proposition. A narrow preemption rule is similar to a strong form of the regulatory compliance defense. It would make FDA approval of drug labeling determinative of non-negligence and non-defectiveness if the FDA considered the specific risk at issue in a case and concluded the labeling provided sufficient warning with respect

to that risk. A state could still impose strict liability that was independent of negligence in failing to give additional warning. In addition, liability would not be precluded if the FDA did not consider the relevant risk in approving the drug and labeling. Thus, a drug-maker would be subject to liability if (as in this case) it had reason to know the labeling was deficient based on post-marketing risk information (e.g., information demonstrating the risk of tardive dyskinesia associated with metoclopramide use) if the FDA had not yet considered whether that information justified additional warning. A drug-maker would similarly be liable for failure to warn about "off-label" uses not approved by the FDA (as in this case, since the FDA did not approve long-term use of metoclopramide). And a drug-maker would be liable if the FDA did not consider the specific risk at issue (as in this case). Additional exceptions might also be made for cases in which a drug-maker withholds relevant risk information to the FDA or unduly influences the FDA's decision.

A broad form of preemption might be similar to the Michigan statute. It would shield a drug-maker from all claims regarding an FDA-approved drug and labeling so long as the drug-maker complied with the FDA's orders. A claim would be precluded even if the FDA did not consider, and could not have considered, the relevant risk when approving labeling. While the Michigan statute makes exception for cases in which a drug-maker withholds crucial risk information, or

in which a drug-maker bribes an FDA official, one could dispense even with those exceptions.

Intermediate possibilities exist. For example, a narrow form of preemption could be supplemented by a rule precluding a state from imposing strict liability. Or drug-makers could be shielded from punitive damages.

Ideally, Congress or, in the absence of congressional action, state legislatures should choose among alternative preemption rules because the choice turns on fundamental questions of morality and policy on which there is deep disagreement, as well as contestable empirical assumptions. The choice only obliquely turns on views of the relative strengths and weaknesses of the FDA and courts in regulating drug warnings.

In particular, Congress can best weigh the interests in corrective justice and compensation, which justify civil liability, against the concerns for litigation cost and error, and the interest in national uniformity, which justify preemption. The political branches are also in the best position to give due weight to the fundamental federalism concerns that would be raised by any effort to preempt such basic and well-established state-law tort principles. Finally, institutional concerns point to Congress. Congress can legislate rules that resolve predictable boundary-drawing problems. This Court can resolve only the particular case before it. It would require a series of

cases to define even the most general contours of preemption.

A possible alternative might be to have the FDA rule on a case-by-case basis, as it approves a particular drug and labeling, whether, and the extent to which, preemption of civil liability is warranted. The agency has done this in the past by rulemaking in specific situations when it deemed it warranted.[16]

Congress should also decide whether a preemption rule applies retroactively or prospectively. It has long been understood that FDA approval of a drug and labeling does not shield a drug-maker from failure-to-warn liability, particularly for risks that the FDA did not consider in approving the labeling. This understanding may have helped persuade FDA officials to approve a drug and its labeling because they knew they were not solely responsible for protecting the public from unreasonably dangerous drugs. Certainly they would not have thought the legal system expected them to be omniscient and to anticipate post-marketing risks and off-label uses. Giving retroactive preemptive effect to decisions that were made in reliance on the understanding that they would not preempt state law is a radical step that warrants the kind of careful consideration that Congress is in the best position to provide.

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[16] Examples are collected at 71 FED. REG. at 3935.

IV. Federal law does not alter the elements of a state-law failure-to-warn case by imposing an additional burden on respondents to disprove petitioners' defenses as part of their affirmative case

Respondents have each brought a typical state-law failure-to-warn case. The elements of such a case are well established. Each respondent must show that she was injured by metoclopramide manufactured by the relevant defendant, that the metoclopramide was sold with inadequate warnings, and that her injuries were caused by the absence of adequate warnings. See, e.g., Restatement (Third) of Torts: Products Liability § 6 (1998); OWEN, *supra* § 11.4.

In Louisiana (the relevant state for respondent Demahy), legislation defines the elements of a product liability failure-to-warn claim against a manufacturer. See La. R.S. 9:2800.54 & .57. Under the applicable statute a "claimant bears the burden of establishing that the manufacturer did not use 'reasonable care' to provide the claimant, or another, with an adequate warning and that the failure to do so proximately caused the claimant's injuries." FRANK L. MARAIST & THOMAS C. GALLIGAN, JR., LOUISIANA TORT LAW 15-30 (2004 & Supp. 2010). Louisiana also recognizes and applies the "learned intermediary" doctrine. La. R.S. 9:2800.53(8); MARAIST & GALLIGAN, *supra* at 15-36. Thus, the Louisiana failure-to-warn claim is a garden variety failure-to-warn claim based in negligence (failure to use reasonable care) and requires that the plaintiff prove causation.

In Minnesota (the relevant state for respondent Mensing), a plaintiff in a failure-to-warn claim must similarly establish the defendant's knowledge of the dangers, that the warnings provided were inadequate, and that the lack of an adequate warning caused the plaintiff's injuries. See *Tuttle v. Lorillard Tobacco Co.*, 377 F.3d 917, 924 (8th Cir. 2004) (applying Minnesota law); *Erickson v. American Honda Motor Co.*, 455 N.W.2d 74, 77-78 (Minn. Ct. App. 1990).

The elements of a failure-to-warn case are so clearly established in Louisiana, Minnesota, and nationwide that petitioner Pliva concedes that "in a typical failure-to-warn case" a plaintiff "needs to show only that (a) the drug is responsible for his or her injuries and (b) the existing warning's alleged inadequacy proximately caused the drug use that precipitated those injuries." Pliva Br. 51.

Pliva seeks to avoid its concession by arguing that these are not typical cases, and that the intricacies of federal law impose an additional obligation on respondents to prove, as part of their affirmative case, what the FDA would have done if petitioners had recommended adequate warnings. See *id.* If Pliva is making an argument about preemption, it is incorrect under *Wyeth*. If Pliva is making an argument about state law and proving causation, it is both wrong and irrelevant.

Pliva's attempt to redefine the elements of a failure-to-warn case misstates products liability law in a fundamental way. As this Court clearly recognized in *Wyeth*, once a plaintiff has established an

affirmative case, the burden is on the defendant to show that under federal law it could not have complied with its state-law duty to warn. See 129 S. Ct. at 1198-99.

Pliva attempts to distinguish *Wyeth* with the argument that Wyeth could have complied with its state-law duty-to-warn requirement (using the CBE procedure) whereas petitioners here cannot comply (because the CBE procedure is claimed to be unavailable to them). See Pliva Br. 51. Even if the premise were correct, Pliva's argument is circular. The burden was on Wyeth because it was seeking to rely on an affirmative defense, not because this Court first concluded that it could comply with both federal and state requirements. Under Pliva's proposed rule, the allocation of the burden would depend on whether or not a party would be able to carry the burden.

Although *Wyeth* did not involve a generic drug, it is nevertheless instructive. This Court expressly noted that the FDA retained its authority to reject labeling changes made through the CBE procedure. Having noted that truism, the *Wyeth* Court continued:

> [A]bsent clear evidence that the FDA would not have approved a change to Phenergan's label, we will not conclude that it was impossible for Wyeth to comply with both federal and state requirements. * * * Wyeth has offered no such evidence.

Id. at 1198; see also *id.* at 1199 ("Wyeth has failed to demonstrate that it was impossible for it to comply with both federal and state requirements."). Thus the *Wyeth* Court did not require a plaintiff seeking to avoid preemption to prove that the FDA would have approved a CBE change. Here, requiring respondents to prove what the FDA would have done if the petitioners had recommended appropriate warnings or "Dear Doctor" letters would be akin to requiring the *Wyeth* plaintiff to prove the FDA would not have rejected a change in the Phenergan label. The Court did exactly the opposite.

Pliva also misconceives the nature of the causation inquiry. The burden is on each respondent to show a sufficient causal connection between the inadequate warnings and her own injury. Each respondent has made sufficient allegations to survive petitioners' motions to dismiss or for summary judgment. Indeed, those motions do not deny the basic causal connection which involve issues of state tort law, not federal preemption. Petitioners do not argue that an adequate warning would have made no difference in how the physician prescribed the drug, which is the relevant causation inquiry. Rather, they argue that it would have been impossible for petitioners to give adequate warnings. Whether this is characterized as a preemption defense or a regulatory compliance defense, it is not an element as to which the plaintiff bears the burden under state law. Pliva points to no basis in federal law for its radical proposal to shift the burden to the plaintiff to disprove

the defendants' affirmative defenses as part of her affirmative case. Consistent with *Wyeth*, proof that the FDA would have rejected a recommendation to give an adequate warning is part of petitioner's affirmative defense. As in *Wyeth*, petitioners have "offered no such evidence." *Id.* at 1198.

CONCLUSION

The judgments of the Courts of Appeals for the Eighth and Fifth Circuits should be affirmed.

Respectfully submitted,

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APPENDIX

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Professor Mark P. Gergen currently teaches at Boalt Hall School of Law, University of California at Berkeley. He has taught and written on the entire spectrum of the law of obligations: contracts, torts, and restitution. He was the reporter for *Restatement (Third) of Torts: Economic Torts and Related Wrongs*.

Jon Hanson is the Alfred Smart Professor of Law at Harvard Law School, where he has been writing about and teaching courses on tort law and products liability law (among other topics) for the last twenty years.

AMICUS CURIAE BRIEF

Supreme Court, U.S.
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IN THE

Supreme Court of the United States

PLIVA, INC., *et al.*, 09-993 *vide* 09-1039, *Petitioners*,

v.

GLADYS MENSING, *Respondent*.

ACTAVIS ELIZABETH LLC, 09-1039 *vide* 09-993, *Petitioner*,

v.

GLADYS MENSING, *Respondent*.

ACTAVIS INC., 09-1501, *Petitioner*,

v.

JULIE DEMAHY, *Respondent*.

On Writs of Certiorari to the United States Courts of Appeals for the Fifth and Eights Circuits

BRIEF OF THE GENERIC PHARMACEUTICAL ASSOCIATION AS *AMICUS CURIAE* IN SUPPORT OF PETITIONERS

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(11)

QUESTION PRESENTED

The Drug Price Competition and Patent Terms Restoration Act (the "Hatch-Waxman Act") allows for the approval of low-cost generic drug products through an abbreviated process that hinges on the requirement that generic drug products—and their warnings—must in all material respects be "the same as" their FDA-approved brand-name equivalents.

Does the Hatch-Waxman Act preempt state-law failure-to-warn claims against the manufacturer of a generic drug whose product warnings were, as the Hatch-Waxman Act and FDA implementing regulations expressly require, "the same as" those FDA approved for the product's brand-name equivalent?

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IN THE

Supreme Court of the United States

NOS. 09-993 *vide* 09-1039, 09-1501

PLIVA, INC., *et al.*, 09-993 *vide* 09-1039, *Petitioners*,

v.

GLADYS MENSING, *Respondent*.

ACTAVIS ELIZABETH LLC, 09-1039 *vide* 09-993, *Petitioner*,

v.

GLADYS MENSING, *Respondent*.

ACTAVIS INC., 09-1501, *Petitioner*,

v.

JULIE DEMAHY, *Respondent*.

On Writs of Certiorari to the United States Court of Appeals for the Fifth and Eights Circuits

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BRIEF OF THE GENERIC PHARMACEUTICAL ASSOCIATION AS *AMICUS CURIAE* IN SUPPORT OF PETITIONERS

INTEREST OF *AMICUS CURIAE* AND SUMMARY OF ARGUMENT

The Generic Pharmaceutical Association ("GPhA") is a non-profit, voluntary association[1] comprised of more

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[1] All parties have consented to the filing of this brief, and letters evincing such consent have been filed with the Clerk. Pursuant to

than 140 manufacturers and distributors in the generic pharmaceutical industry. GPhA members provide American consumers with generic pharmaceutical medications that are just as safe and efficacious as their brand-name counterparts, but at a fraction of the cost. Generic drugs today account for nearly 70% of all prescription pharmaceuticals dispensed in the United States each year, providing access to safe and affordable medicines for more Americans, including the poor and elderly, than ever before.

The matters now before the Court are representative of thousands of product liability lawsuits currently pending against GPhA members across the country. The essential thrust of those suits is to misapply this Court's recent decision in *Wyeth* v. *Levine*, 129 S.Ct. 1187 (2009), to subject generic drug manufacturers to the same post-marketing surveillance and labeling requirements applicable to brand-name manufacturers without regard to the ruinous costs this would impose on the generic pharmaceutical industry—costs that Congress explicitly sought to eliminate for the express purpose of increasing the availability of low-cost generic drugs.

The generic pharmaceutical industry has been shaped by congressional and regulatory oversight for specific public purposes—to make medicines available to as many people as possible at the lowest possible costs without introducing additional safety risks. Those purposes have been achieved. Generic drugs are required to be no more than exact copies of brand-name drugs that already have been subjected to the thorough testing process required

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this Court's Rule 37.6, *amicus* states that no counsel for a party authored any part of this brief and that neither such counsel, nor any party, nor any person or entity other than *amicus*, its members, or its counsel made a monetary contribution intended to fund the preparation or submission of this brief.

by the Food and Drug Administration ("FDA"). Generic manufacturers *cannot* change their labeling under federal law; only FDA can do that. Nor can generic manufacturers reinvent the expensive research and testing FDA required to approve the brand drug, all of which was complete many years before the generic version could even be produced. Recreating that wheel would eliminate the key benefit of generic drugs—that they are low cost without new risk.

This is common sense, but it is not only that. It is the regulatory regime purposefully adopted by Congress and FDA. Upsetting that regulatory balance by exposing generic manufacturers to state tort liability will adversely affect the industry, drive up costs for no salutary purpose, and contravene the intent of the political branches of government. It would return the generic pharmaceutical industry to its condition *before* Congress specifically authorized abbreviated approval conditioned on the "sameness" between the brand drug and the generic drug. That would also return the United States to a time when producing low-cost alternatives to brand drugs was economically unfeasible. It would, in short, threaten the continued availability of affordable generic drugs in America.

ARGUMENT

I. Divesting Generic Drug Manufacturers of Labeling Authority and Responsibility Is an Integral Part of a Carefully Calibrated Congressional Policy to Make Generic Drugs Widely Available by Ensuring that Generic Drugs Are Identical to Branded Drugs

Contemporary regulation of generic drugs has developed along a trajectory steeped in experience. Generic drugs are not simply "cheaper" drugs, in the sense that they are lesser in quality or in any other meaningful way.

Rather, they are cheaper—and intentionally so—precisely because they are *the same* as the name-brand drugs which have been subjected to the extraordinarily intensive testing required in the United States. To be a generic drug, the key requirement is that it be *identical* to the brand drug in all material respects. Generics rely on the intensive testing and approval process for the brand drug; in exchange, they forfeit any ability to modify the contents of the brand drug or the labeling that must accompany it. A brief survey of how Congress established the current regulatory regime, which divides brand-name drugs from their generic equivalents, demonstrates why it makes no sense to hold generic drug manufacturers liable in tort for actions that are beyond their control.

A. Congress has determined that generic drugs must be identical to the brand drugs they duplicate

Congress laid the foundation for the modern pharmaceutical regulatory scheme in 1962 by amending the Food, Drug and Cosmetic Act ("FDCA") to require that *all* drugs marketed in the United States must be approved by FDA as both safe and effective. H.R. Rep. No. 98-857(I) (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647, 2649 (hereinafter "H.R. Rep."), Pet. App. 124a.[2] Every manufacturer of a drug first marketed after 1962 was required to conduct clinical studies to demonstrate safety and efficacy. *Id.* at 124a-125a. This costly and time-consuming testing requirement applied equally to both branded drugs and generic versions. *Ibid.*

FDA mitigated the inefficiencies in this regime by developing an abbreviated procedure for "duplicate" ver-

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[2] All references to "Pet. App." are to Appendix accompanying the petition for a writ of certiorari in No. 09-993, *Pliva, Inc., et al.* v. *Mensing*, No. 09-993.

sions of previously approved branded drugs. If the "duplicate" was bioequivalent to, or the "same as," the branded drug, the abbreviated process dispensed with duplicative clinical studies. "FDA considers such retesting to be unnecessary and wasteful because the drug already had been determined to be safe and effective" through testing submitted by the brand manufacturer. *Id.* at 124a.

In 1984, Congress explicitly adopted—and expanded upon—this common-sense approach. The Hatch-Waxman Amendments to the FDCA ("Hatch-Waxman") codified FDA's abbreviated procedure for approval of duplicate drugs and authorized its use for all generic drugs. See generally 21 U.S.C. § 355(j); Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28,872, 28,873 (proposed July 10, 1989). Hatch-Waxman exempts generic drug manufacturers from the extensive and costly testing and reporting requirements applicable to manufacturers of new, and therefore untested, drugs. It authorizes FDA to approve a proposed generic drug if its manufacturer can demonstrate that the generic product is bioequivalent to a branded drug previously approved by FDA as safe and effective. See 21 U.S.C. § 355(j)(2)(A); 21 C.F.R. § 314.92(a)(1). Specifically, the generic manufacturer must show that its drug is the *same as* the branded drug with respect to active ingredient, route of administration, dosage form, strength, conditions of use and—most importantly here—labeling. See 21 U.S.C. § 355(j)(2)(A); 21 C.F.R. § 314.92(a)(1).

B. Congress' purpose was to decrease healthcare costs—and it has succeeded, beyond Congress' wildest expectations

The intended consequence of precluding any variation between generic drugs and the approved brand drug was to foster vigorous price competition among generics. Hatch-Waxman had a clear and overriding purpose—to

increase the availability of low-cost generic drugs, with the twin benefits of decreasing healthcare costs for everyone and increasing access to quality medical care for millions of poor and elderly Americans. Simply stated, the essential point of Hatch-Waxman was "to get generic drugs into the hands of patients at reasonable prices—fast." *Andrx Pharms., Inc.* v. *Biovail Corp. Int'l*, 256 F.3d 799, 809 (D.C. Cir. 2001) (internal quotation omitted).

Congress estimated that Hatch-Waxman would "make available almost immediately nearly twice as many low-cost, generic drugs as are now available." 130 Cong. Rec. H24456 (daily ed. Sept. 6, 1984) (statement of Rep. Douglas Walgren), Pet. App. 142a. Further, the increased availability of affordable generic drugs "would save American consumers $920 million over the next 12 years." H.R. Rep., Pet. App. 125a. Congress further projected that federal and state governments both would reap the benefits of increased generic competition through substantial savings in government assistance programs, noting that the federal government alone spent approximately $2.4 billion for drugs in 1983 in Medicaid and Veterans Administration programs. *Id.* at 127a.

Beyond the significant overall cost savings, Congress also recognized that increasing the availability of affordable generic drugs would materially improve the quality of medical care available to poor and elderly Americans.

> [T]here are many post-1962 drugs that are off patent for which there is no generic competition. Drugs in this category, taken from a list of the top 100 prescribed drugs, have a drugstore market value of $500 million * * * Who is hurt by delay? The elderly, the 11 percent of the population who purchase 25 percent of all drugs.

New Drug Application: Hearing on H.R. 3605 Before the Subcomm. on Health and the Env't of the H. Comm. on Energy and Commerce, 98th Cong. 43 (1983) (statement of Kenneth Larsen, chairman of the Generic Pharmaceutical Industry Association). Evidence presented during committee hearings revealed:

> in stark human terms what it means to pay high prices for drugs, when FDA-approved identical generics could be available at a fraction of the price * * * The choice, for them, is horrendous. Do you stop taking drugs at the end of the month, or do you skip some meals, or do you fail to heat your house and wait out the month in the cold? Those are the realities. Unless Congress provides an effective procedure for approving post-1962 drugs, consumers, particularly the elderly, are left with the hard choices.

Id. at 44. "For these older Americans this bill will ease the Hobson's choice between spending fixed incomes on pharmaceuticals or other necessities." Pet. App. 115. As President Reagan said at the time, Hatch-Waxman would assure that "the American people will save money, and yet receive the best medicine that pharmaceutical science can provide." Presidential Statement on Signing S. 1538 Into Law, 20 Weekly Comp. Pres. Doc. 1359, 1360 (Sept. 24, 1984) (quoted in *Glaxo, Inc.* v. *Novopharm, Ltd.*, 110 F.3d 1562, 1568 (Fed. Cir. 1997)).

The reality of Hatch-Waxman has far exceeded the projections of even its most optimistic proponents. The Congressional Budget Office (CBO) reported in 1998 that savings realized from the substitution of generic for brand-name drugs saved consumers between $8 billion and $10 billion in 1994 alone, the tenth year after the enactment of Hatch-Waxman. Congressional Budget Office, How Increased Competition From Generic Drugs

Has Affected Prices and Returns in the Pharmaceutical Industry 13 (1998) (hereinafter "CBO 1998").[3]

Since then, annual savings have grown exponentially. A second study by the CBO revealed that generic drug use in 2007 saved seniors and the federal government $33 billion just on Medicare Part D prescription drug costs. Congressional Budget Office, Effects of Using Generic Drugs on Medicare's Prescription Drug Spending 7-8 (2010) (hereinafter "CBO 2010").[4] Another recent study of prescription drug use in the U.S. found that dispensing generic versions of brand name drugs saved the American healthcare system more than *$824 billion* over the past decade (2000-2009) and *$139.6 billion in 2009 alone*. Generic Pharmaceutical Association, Savings Achieved Through the Use of Generic Pharmaceuticals 2000-2009 1-2 (2010) (hereinafter "GPhA 2010").[5] The savings projected by the proponents of Hatch-Waxman—$920 million over the first 12 years—are now being achieved *every three days*.

The impact of generic competition on overall drug prices is dramatic and escalating. By 1998, the average retail price of a prescription for a generic drug had fallen to half the cost of a multi-source brand-name drug ($17.40 vs. $37.40).[6] *See* CBO 1998 at 31. Today, the average generic drug costs barely a quarter of its branded counterpart. CBO 2010 at 8-9. A 2009 IMS National

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[3] Available at http://www.cbo.gov/ftpdocs/6xx/doc655/pharm.pdf.

[4] Available at http://www.cbo.gov/ftpdocs/118xx/doc11838/09-15-PrescriptionDrugs.pdf.

[5] Available at http://www.gphaonline.org/sites/default/files/GPhA%20Savings%20Study%20Book%20Updated%20Web%20FINAL%20Jul23%2010_0.pdf

[6] A multi source brand refers to a drug that is sold under a brand name but is also available in generic versions from other manufacturers. CBO 1998 at 31.

Prescription Audit demonstrated this dramatic difference by comparing what the typical insurance or government formulary charges today:

- $6 for generic medications;
- $29 for preferred brand drugs; and
- $40 for non-preferred brand drugs.[7]

Aitken et al., Prescription Drug Spending Trends in the United States: Looking Beyond the Turning Point, 28 Health Affairs, no. 1, w151, w155 (2009).

The increased availability of low-cost generic drugs also has fulfilled Hatch-Waxman's second, and perhaps most important, goal: increased access to quality medical care for millions of Americans, particularly the poor and elderly. As the CBO noted in its 1998 study:

> The Hatch-Waxman Act has increased the likelihood that generic copies will become available once the patent on a brand-name drug expires. Before the act (in 1983), only 35 percent of the top-selling drugs no longer under patent had generic copies available. Today, nearly all do.

CBO 1998 at xii. Affordable generic alternatives are available today in virtually every important therapeutic class, including such drugs as oncology and cardiovascular medicines that were once priced far beyond the means of many Americans. GPhA 2010 at 3. For many Americans, the increased availability of affordable generic alternatives literally can mean the difference between receiving quality medical care or receiving none, as

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[7] A preferred drug refers to a drug that is authorized for use under an insurance or government plan and thus may dispensed without additional approvals. A non-preferred drug, on the other hand, may be dispensed to a patient only after special approval is obtained. See, e.g., Texas Health and Human Services Commission, Texas Medicaid/CHIP Vendor Program, Prior Authorization Program, available at http://www.hhsc/state.tx.us/hcf/vdp/pt/pa_program.html.

shown by a recent AARP survey in which fully a quarter of seniors reported not being able to afford a prescription drug when no generic was available. See FDA, Greater Access to Generic Drugs: Special Report From the FDA Consumer Magazine and the FDA Center for Drug Evaluation and Research (4th ed. 2006).[8] Moreover, government assistance programs, such as Medicaid, now can help more Americans at lower cost.

> Data from the federal Centers for Medicare and Medicaid Services (CMS) show that in 2009 about 290 million prescriptions were purchased through the Medicaid program at a total cost of $23 billion. The availability of generics enabled Medicaid to purchase 64% of these prescriptions (186 million) by using just $3.9 billion of the $23 billion spent for drugs. *In other words, Medicaid met nearly two-thirds of its prescription drug need with less than one-fifth of its prescription dollars.*

GPhA 2010 at 4 (emphasis added). Similarly, the CBO found that although generics constituted fully 65% of prescriptions dispensed under Medicare Part D in 2007, they accounted for only 25% of total prescription drug costs. CBO 2010 at 12.

C. The low generic prices Congress desires depend upon the low costs of market entry made possible by Hatch-Waxman

The savings described above result from a system in which a new drug is rigorously scrutinized through exacting FDA requirements, given a profit-making period of patent exclusivity, and then—once the regulatory approval is set and the patent has expired—allowing replication of that drug by manufacturers who must certify that the generic version is identical to the name-brand

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[8] Available at http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143545.htm

version. This system treats generic manufacturers as just that—manufacturers, not inventors or testers—and thereby keeps their market-entry costs low.

The prices for generic drugs are linked directly to the costs of market entry, and several features of Hatch-Waxman work together to reduce the market entry costs for new generic drugs. First, the ANDA process eliminates the duplicative, unethical[9] and expensive testing requirements that formerly were necessary to obtain approval for a generic copy of a previously approved innovator drug. H.R. Rep., Pet. App. 124a. As the CBO put it:

> The Hatch-Waxman Act streamlined the process for approving generic drugs by requiring only that manufacturers demonstrate "bioequivalence" to an already-approved innovator drug. (Bioequivalence means that the active ingredient is absorbed at the same rate and to the same extent for the generic drug as for the innovator drug.) The tests necessary to prove bioequivalence are much less costly than those required to prove safety and efficacy.

CBO 1998 at xii.

Second, Congress required that a generic drug be "the same as" the branded drug with respect to active ingredient, route of administration, dosage form, strength and conditions of use recommended in the label. 21 U.S.C. § 355(j)(2)(A). And in codifying FDA's streamlined ANDA scheme, Congress expressly adopted FDA's policy of using the term "same as" for the equivalency required for generic drug approval:

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[9] In exempting generic manufacturers from the need to perform duplicative clinical trials, Congress recognized that "such retesting is unethical because it requires that some sick patients take placebos and be denied treatment known to be effective." H. R. Rep., Pet. App. at 124a.

> The committee has adopted the FDA's policy of utilizing the terms "same" except that the bill permits an ANDA to be approved for less that all of the indications for which the listed drug has been approved as explained below.

H.R. Rep., Pet. App. 131a. Of particular relevance here, Congress likewise preserved the "same as" requirement for the labeling of the generic drug by requiring that an ANDA must contain adequate information "to show that the labeling proposed for the [generic] drug is the same as the labeling approved for the listed drug * * *." 21 U.S.C. § 355(j)(4)(G).

The streamlined testing and labeling requirements for generic medications have dramatically reduced the costs of market entry. For the average new drug that was first tested in humans during the 1970s and early 1980s, its producer had spent $114 million (in 1987 dollars) on development and testing. DiMasi, Cost of Innovation in the Pharmaceutical Industry, 10 J. of Health Econ. 107, 132 (1991). Today, the cost to bring a new branded drug to market typically exceeds a billion dollars. U.S. Department of Health and Human Services, Office of the Assistant Secretary for Planning and Evaluation, Office of Science and Data Policy, ASPE Issue Brief, Expanding Use of Generic Drugs 4-5 (2010) (hereinafter "ASPE Issue Brief").[10] By contrast, the research and development costs for a generic drug are about *one-tenth of one percent* as much—only 1 to 2 million dollars (although those costs have risen significantly as well).[11] *Ibid.*

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[10] Available at http://aspe.hhs.gov/sp/reports/2010/GenericDrugs/ib.shtml.

[11] The costs of entry for generics, while still dramatically lower than for brand-name entrants, have also increased substantially over time. The average research and development costs for a new generic

The explanation for this thousand-fold difference in preliminary costs is obvious:

> Because they can reverse-engineer an innovator drug, and need not repeat safety and effectiveness studies, generic manufacturers can bypass the time and costs to develop a new drug and bring a drug to market with a much smaller investment.
>
> • • •
>
> The relatively low costs to entry for generic drugs lead to increased competition, which drives prices for generic drugs down dramatically.

ASPE Issue Brief at 3, 5.

Low cost of entry affects generic prices in another important way—it increases competition. The price difference between brand and generic drugs is directly related to the number of generic entrants to the market. When FDA analyzed the impact of generic drug entry on average prices for generics (as a percentage of the price for the brand drug) in 2005, it found that the first generic entrant has a relatively small effect on price, but subsequent entrants dramatically reduce the average relative price. ASPE Issue Brief at 5; Figure 1, *infra*. With only one entrant, the generic price averaged fully 94% of the brand price, but even a single additional generic competitor cut the price in half. The entry of four more dropped the generic price to only a quarter of the brand. *Id.* The low cost of generic drugs is dependent upon robust competition created by the low cost of market entry.

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drug were approximately $338,000 in the period immediately following passage of the Act but grew to approximately $608,000 a decade later. See Reiffen & Ward, Generic Drug Industry Dynamics 4 (Fed. Trade Comm'n, Working Paper, 2003), available at http://www.uta.edu/faculty/mikeward/GenericDynamics.pdf.

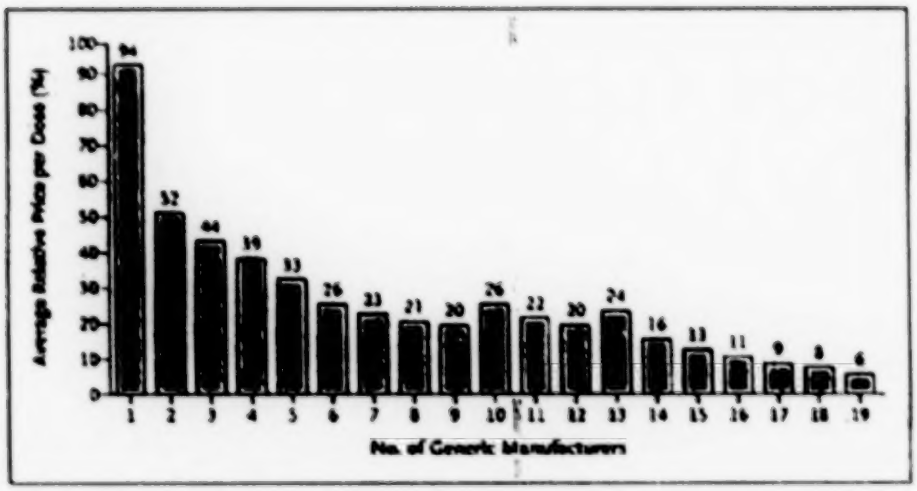

Figure 1: Change in the Average Relative Price of a Drug as the Number of Generic Versions Increases. The average relative price is the average price of a generic version divided by the price of the brand-name drug. Data are from an FDA analysis of retail sales data from IMS Health. Frank, Perspective: The Ongoing Regulation of Generic Drugs, 357 New Eng. J. Med. 1993, 1995 (2007).

The streamlined regulatory scheme for generic drugs established by Hatch-Waxman is central to this economic model. America has already seen the consequences of imposing the full regulatory and economic burden on generics:

> Before 1984, generic-drug makers were obliged to conduct the same safety and efficacy tests that had been required of the original brand-name manufacturers to receive Food and Drug Administration (FDA) approval for marketing. These provisions often rendered it noneconomical to bring a generic to market. The Hatch–Waxman Act changed all that.

Frank, Perspective: The Ongoing Regulation of Generic Drugs, 357 New Eng. J. Med. 1993, 1993-1994 (2007).[12]

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[12] Available at http://www.nejm.org/doi/full/10.1056/NEJMp078193.

In enacting this statutory scheme, Congress in effect created the modern generic pharmaceutical industry. Congress enhanced the availability of generic medications by eliminating unnecessary costs of entry. And—as described in greater detail below—it did so without any threat to public health (because the "same as" requirement ensures that generics are precisely the same as medicines already fully approved for public use, and which would be used by all patients but for cost). Generics introduce no new risks to the public, but they substantially expand the availability of affordable drugs to those who need them most.

D. The statutory requirement that a generic drug be the "same as" its brand counterpart provides adequate assurances of safety

The central requirement of "sameness" not only provides the generic manufacturer with a clear blueprint for development but also assures FDA and the public that the generic drug is safe and effective. "In the case of drugs which are the same as the listed drug, the focus of the bill is to provide * * * FDA with sufficient information to assure that the generic drug is the same as the listed drug that has previously been determined to be safe and effective." H.R. Rep., Pet. App. 130a. See also 57 Fed. Reg. 17,950, 17,951 (April 28, 1992) (establishing procedures for duplicates of post-1962 drugs). As the Fifth Circuit noted in *Demahy*, FDA's own guidelines for generic drug labeling are premised on the policy that "[c]onsistency among generic and name brand manufacturers not only avoids redundant research and monitoring efforts, it also assures consumers and physicians that the generic product is safe and effective." JA561.

The *Demahy* Court certainly was correct when it noted that "Congress did not consider the Hatch-Waxman Amendments in a vacuum." JA561. Indeed, Congress recognized that to achieve the goal of increas-

ing the availability of prescription drugs that are *both* safe and effective *and* low-cost, the ANDA scheme had to reflect the fact that brand and generic manufacturers play fundamentally different roles in the drug development process. A new brand-name drug enters the market under the protection of a period of patent exclusivity during which it constitutes the entirety of the market. The brand drug reaches the market in the first instance only after FDA concludes that it is safe and effective based on an extensive program of animal toxicology and human clinical trials. The brand manufacturer thereafter maintains market approval for its drug by complying with any post-approval requirements of FDA, which often include additional clinical trials to support new indications or formulations of the drug or to satisfy additional safety or efficacy concerns raised by FDA. See 21 C.F.R. § 314.510; FDA, Center for Drug Evaluation and Research, Guidance for Industry: Postmarketing Studies and Clinical Trials—Implementation of Section 505(o) of the Federal Food, Drug, and Cosmetic Act 2-3 & nn. 3-4 (2009) (describing FDA authority to require post-marketing studies).

The brand manufacturer also must conduct extensive post-marketing surveillance that encompasses review and analysis of reported adverse events and published medical and scientific literature—an analysis that is conducted against the backdrop of knowledge obtained through the clinical trials and other research conducted to obtain approval in the first place. See 21 U.S.C. § 355(k); 21 C.F.R. § 314.80. During this period of patent exclusivity, the brand manufacturer thus effectively has a monopoly, not only on the market for the drug, but also on the accumulated medical and scientific knowledge of its safety and efficacy, which it shares with FDA pursuant to the comprehensive federal scheme of post-marketing surveillance and reporting regulations.

It is only after the expiration of this period of market exclusivity for the brand—which typically can last as long as 14 years[13]—that the first generic manufacturer can apply for FDA approval to enter the market. Generic entry thus begins only after the therapeutic and safety profile of the drug is well understood by the brand manufacturer and FDA—and, perhaps more importantly, by the medical community and consumers—based on many years of study, regulation and use. As the *Demahy* court recognized:

> In the world of prescription drugs, a pharmaceutical company manufactures, and the FDA approves, a branded drug only after extensive research and testing. Pioneer drug manufacturers thus develop superior knowledge of their product * * * Conversely, generic manufacturers undertake limited research efforts thanks to Hatch-Waxman. They can obtain approval for their copycat drug and label with the limited showing that their product is the "same as" a branded drug * * * That difference in initial regulatory burdens marks a *stark tension between Hatch-Waxman's quest to quickly and cheaply place generic drugs on the market and a state law tort regime* that represents the lone remedy for individuals harmed by inadequate labeling of generic drugs.

JA560-61 (emphasis added).

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[13] As the APSE Issue Brief put it, "[p]atents are issued by the U.S. Patent Office and offer 20 years of protection from competition. However, sponsors typically apply for a patent early in the drug development process and so many of the years of patent protection will be expended before the drug reaches the market. The Hatch-Waxman Act offers restoration of some of the years of patent protection expended during clinical testing and FDA review. Up to five years of patent term may be restored, with the total patent time after FDA approval limited to 14 years." APSE Issue Brief at 9.

Moreover, unlike the branded regime, which contemplates a market restricted to one drug, the Hatch-Waxman scheme is designed to encourage the market entry of as many generic competitors as is economically feasible. See *infra* Part I.C. The generic market that emerges following the expiration of the branded monopoly thus is, by design, highly fragmented. Although the overall generic market share will grow relative to the brand as more generic competitors enter the market, no single generic manufacturer will ever achieve anything approaching the market dominance initially enjoyed by the brand. Indeed, it is the essential fungibility between generic and brand, and among generics, that provides the assurance of consistency of safety and efficacy across the entire market.

Just as any one generic manufacturer can capture only a portion of the market for a drug, so too can any one manufacturer accumulate only a piece of the safety data for the drug. For example, generic drug manufacturers receive relatively few adverse event reports ("AERs") following approval of their products—far fewer, certainly, than are received by the brand manufacturer and FDA. See FDA, Center for Drug Evaluation and Research, Office of Generic Drugs, Manual of Policies and Procedures, Handling of Adverse Experience Reports and Other Generic Drug Postmarketing Reports 1 (2005)[14] (noting Office of Generic Drugs receives few AERs since the reports frequently do not identify a generic manufacturer for the drug and because the safety profile of a drug is well-known before generic versions are approved). Further, because generic manufacturers do not have the comprehensive scientific data necessary to perform a meaningful analysis of reported adverse

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[14] Available at http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm079791.pdf.

events, FDA requires only that they submit to the agency the limited post-approval reports they actually receive and maintain adequate records. See 21 C.F.R. § 314.94. Moreover, FDA does not require generic drug manufacturers to affirmatively survey scientific literature. See 21 C.F.R. § 314.80(b).[18] After all, such a requirement would only increase costs to no meaningful end.

II. HATCH-WAXMAN PREEMPTS STATE TORT LIABILITY FOR LABELING

FDA has implemented a comprehensive regulatory scheme for generic drugs that is carefully designed to achieve the goal of Hatch-Waxman: to allow the generic industry to produce medicines with the same therapeutic benefits as brand-name drugs, but at a fraction of the cost. At its core is the unerring policy that generic drug products and their warnings must be "the same as" their brand-name equivalents. By misapplying this Court's recent decision in *Wyeth*—a decision construing FDA's regulations for *branded* drugs, which reflect an entirely different set of public health objectives—the decisions of the courts below undermine the very foundation of Hatch-Waxman by subjecting generic manufacturers to the threat of state tort liability unless they do what federal law expressly prohibits them from doing.

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[18] 21 C.F.R. § 314.80(b) requires "applicants" to promptly review all adverse drug experience information obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience, post-marketing clinical investigations, post-marketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers. But such "applicants" are only those under § 314.50 or § 505(b)(2)—both of which sections apply only to *branded* NDA applicants.

A. State tort liability is inconsistent with Hatch-Waxman's "same as" requirement, under which only FDA may regulate the content of generic drug labeling

It would be something of a Catch-22 for a manufacturer to be held liable under state law for inadequate labeling, given that it would be a violation of federal law for the manufacturer to tinker with the label (and contrary to the principles described above for a generic manufacturer to undertake the sort of duplicative research even to generate data that *might* result in modification of a label). But that would be the consequence of affirming the judgments below.

1. FDA has, in fact, made clear that the labeling for generic drugs is controlled by the agency, not by the generic manufacturers. For example, FDA issued a "Policy and Procedure Guide" shortly after the adoption of Hatch-Waxman, which provides that generic manufacturers cannot unilaterally revise their product labels but instead must await instruction from the agency before making any change to warnings, precautions, or similar labeling. See FDA, Division of Generic Drugs, Changes in the Labeling of ANDAs Subsequent to Revision of Innovator Labeling, Policy and Procedure Guide No. 8-89 (1989).

That this is the law governing manufacturers should be dispositive, but FDA's approach also makes good sense. FDA has recognized that the fragmented nature of the generics market, where multiple competitors each possess only a portion of the accumulated safety data for a drug, makes unilateral labeling changes both impractical and counterproductive:

> [E]ach time there is a change in the innovator's labeling, it could necessitate similar changes in the labeling of as many as 20 or 30 generic drug prod-

> ucts. A change in any section of the package insert of the innovator's product, particularly an important change, e.g., in WARNINGS, PRECAUTIONS, CONTRAINDICATIONS OR DOSAGE AND ADMINISTRATION, triggers action by the Labeling Review Branch to request submission from all generic manufacturers of that drug product. Prompt accomplishment of the revision process is important to assure that consistency is found in the labeling of all similar drug products.

Id. at 1. FDA has recognized that uniformity of brand and generic labeling is essential "to minimize any cause for confusion among healthcare professionals and consumers as well as to preclude a basis for lack of confidence in the equivalency of generic versus brand name drug products."[16] *Ibid.* And FDA has since reiterated this requirement of strict uniformity of labeling many times—in its 1992 Final Rule[17] and its response to public comments thereto,[18] in its 1999 guidance for industry,[19]

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[16] This latter concern—the prospect that labeling variation might undermine public confidence in generic drugs—is a very real and serious concern. Perhaps the greatest barrier to the adoption of generic drugs is the persistent misconception that generic drugs are somehow inferior to their brand-name equivalents, and both FDA and the generics industry spend millions of dollars each year to reassure consumers that affordable generic drugs really are—as federal law requires them to be—the *same as* their more expensive brand-name counterparts. See, *e.g.*, FDA, Facts and Myths About Generic Drugs (2009), available at http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/ucm167991.htm

[17] See 21 C.F.R. §§ 314.93(a), 314.94(a)(8), 314.127(a)(7).

[18] See, e.g., 57 Fed. Reg. 17,961, cmt. 40 ("FDA disagrees with the comments [suggesting that ANDA applicants be permitted to deviate from the labeling for the reference listed drug] * * *. [T]he ANDA product's labeling must [be] the same as the listed product's

and in its response to public comments on its 2006 Final Rule.[20]

2. As clear as FDA has been about these principles, the Brief for the United States as *amicus curiae* filed at the petition stage in this case articulates them at least as clearly (cited hereinafter as "U.S. Br."). Indeed, the brief of the United States not only confirms unequivocally that the content of generic drug labeling is a matter within the exclusive regulatory authority of FDA but also highlights the folly of injecting state tort law into that determination.

In reviewing the labeling regulations applicable to generic manufacturers, the United States first confirms the fundamental principle that "[t]he holder of an approved ANDA is not free to change its approved labeling at will." U.S. Br. 12. The United States then acknowledges that "no formal supplement process under 21 C.F.R. 314.70 (2001) [is] expressly available" to generic drug manufacturers to unilaterally change their product labeling. *Id.* at 15. Specifically, the United States confirms two key limits:

- The Changes Being Effected ("CBE") process of 21 C.F.R. § 314.97 is not available to generic manufacturers because that provision must be read in conjunction with the many regulations that

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labeling because the listed drug product is the basis for ANDA approval.")

[18] See FDA, Center for Drug Evaluation and Research, Guidance for Industry, Changes to an Approved NDA or ANDA at 20 (1999) (requiring that all labeling changes for ANDA drugs must be consistent with section 505(j) [21 U.S.C. § 355(j)(4)(G)], which requires generic labeling to be the "same as" that of the brand).

[20] See 71 Fed. Reg. 3922, 3928 (Jan. 24, 2006) (revising certain labeling format requirements and directing that a generic manufacturer must adhere to the format of the labeling of the brand drug, even if that format does not comply with the new formatting requirements).

require generic drug labeling to be the "same as" that of the brand drug. U.S. Br. 13 (citing 21 C.F.R. § 314.94(a)(8)(iii), 21 U.S.C. § 355(j)(4)(G) and 21 C.F.R. § 314.150(b)(10)).

- The Prior Approval Supplement ("PAS") procedure "also was not expressly available to petitioners to make the labeling change respondent seems to envision," because the CBE process is the exclusive procedure applicable to added or strengthened warnings. U.S. Br. 14.

Next, the United States refutes respondents' assertion that generic drug manufacturers may unilaterally send Dear Health Care Provider ("DHCP") letters warning of product risks inconsistent with those reflected in the labeling for the brand product. U.S. Br. 17. After noting that nothing in the regulations categorically forbids sending such correspondence, the United States observes:

> Nonetheless, ANDA holders do not customarily send DHCP letters without coordinating with FDA. Apart from the practical benefits to coordinating with FDA, *ANDA holders also operate under a regulatory constraint*. DHCP letters sent by a generic manufacturer could potentially affect perceived therapeutic equivalence of the generic drug and its RLD [branded] counterpart * * * *Depending on its content, a DHCP letter from an ANDA holder could inaccurately imply therapeutic differences between the generic drug and its RLD that do not exist, and therefore be misleading.*

Ibid. (emphasis added). Contrasting a letter advising of a manufacturing defect with another letter warning about health risks, the United States observes that the former would not be misleading with respect to the therapeutic equivalence of the generic drug to the brand, while the

latter correspondence could be misleading: "[A]n ANDA holder's letter warning about risks seemingly unique to its product could mislead consumers and providers into believing that the generic drug and RLD were not therapeutic equivalents." *Id.* at 17-18. The United States notes finally:

> Respondent seems to envision DHCP correspondence of the latter sort, which would likely be misleading. *State law may not impose liability on an ANDA holder for failing to send such a letter unilaterally.*

Id. at 18 (emphasis added).

The United States concludes that "FDA mediates the channels available to an ANDA holder under federal law for disseminating strengthened warnings." U.S. Br. 18. This, of course, has been FDA's position from the outset: "After approval of an ANDA, if an ANDA holder believes that new safety information should be provided, it should provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised." *Id.* at 15-16 (quoting 57 Fed. Reg. 17,961, the preamble to FDA's final rule implementing the ANDA application process). That means in the instant case, in the words of the United States, that "*absent FDA's assent, petitioners could not lawfully have disseminated their product with the sort of warning respondent seems to propose.*" *Id.* at 19 (emphasis added).

The Court should spare generic manufacturers (and the American people, who ultimately absorb the transaction costs foisted upon the industry) the Catch-22 that respondents would gladly impose upon them. Generic labeling is the province of FDA, not state courts, and for the reasons expressed in Part I, it is essential to the ful-

fillment of Hatch-Waxman's purposes that it stay that way.

B. The consequences of finding no preemption of tort liability would undo the very structure of the industry that Congress has carefully created

Given the statutory and regulatory background, and the inconsistency between state supervision of labeling (as respondents demand) and exclusive federal control of labeling (as federal law requires), members of GPhA can reasonably ask this question: Where does this leave us when faced with precisely the sort of state tort law claim respondents assert here, and what role can state tort law play in regulating the content of a generic drug label consistent with Congress' intent in adopting Hatch-Waxman and FDA's purpose in implementing it?

1. Unfortunately, on this point, the courts below, and the United States here, are all over the map. All of their answers would distort the industry without warrant from the Act and without any salutary gain for the public. None of these answers recognizes that the question is simply preempted, leaving no role for state courts:

- The Fifth Circuit's opinion in *Demahy* concludes that generic and branded products must be "the same" *only* on the date FDA first approves the generic product; that, thereafter, the generic manufacturer is free to change the label at will. JA534-35. That conclusion is plainly wrong, at least if one assumes that the United States and FDA understand their own regulations. Certainly, it flies in the face of everything FDA has ever said on the subject and what the United States says here, and FDA's implementing regulations are entitled to substantial deference. See

Chevron U.S.A., Inc. v. *Natural Res. Def. Council, Inc.*, 467 U.S. 837 (1984).

- The Eighth Circuit's opinion in *Mensing* correctly acknowledges that "generic labels must be substantively identical to the name-brand label even after they enter the market," and that generic manufacturers thus may not unilaterally change their labeling. JA409. But apart from the singularly unhelpful suggestion that the generic manufacturers simply quit the business altogether,[21] the court posits only that manufacturers could at least *propose* a label change, which the FDA could approve or not at its sole discretion. JA409-10.
- Perhaps recognizing that the ability of a generic manufacturer to propose a label change is a far cry from the power to actually make the change, especially since the latter authority rests exclusively with FDA, the United States suggests a scheme, governed by state tort law, which would ignore the product labeling altogether. Under this scheme, the question of state tort liability would turn, not on the manufacturer's "failure to communicate warnings to their customers (something ultimately in FDA's control)," but rather on their "failure to *take steps* to warn their customers." U.S. Br. 19 (emphasis original). The question thus would be, not what the labeling said, but "what action FDA would have taken in response to a *hypothetical* warning proposal" from the manufacturer.

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[21] It is difficult to conceive a pronouncement more at odds with the clear intent of Congress in adopting Hatch-Waxman to encourage the availability of affordable generic drugs than the *Mensing* court's suggestion that "if [the generic manufacturers] realized their label was insufficient but did not believe they could even propose a label change, they could have stopped selling the product." JA416.

> *Ibid.* (emphasis original). Moreover, the United States contends that in proving this purely hypothetical question, the *manufacturer* "would bear the burden of 'show[ing] the likelihood of FDA *in*action.'" *Ibid.* (quoting JA414-15 (emphasis original)).

The problem with this last approach, of course, is that the pivotal liability question to be decided under state tort law—namely, what FDA would have done in response to a hypothetical warning proposal—is fundamentally not one of fact, but rather one of federal regulatory law and public healthcare policy. In a conventional product liability action, the jury is asked to resolve the factual question of what the consumer would have done, under the particular circumstances attending his use of the product, had the manufacturer provided adequate warnings of the product's dangers. In the case of a prescription drug, the fact inquiry shifts under the learned intermediary doctrine to the prescribing physician, but the essential question remains the same: What would the prescribing physician have done, under the particular circumstances of his treatment of this particular patient, had the manufacturer provided adequate warnings of the product's dangers? In each instance, the operative question is one of fact determinable from evidence of the particular circumstances existing as between that particular plaintiff and that particular defendant at that particular point in time.

The liability question posited here—the hypothetical inquiry into the mind of FDA—is a fundamentally different endeavor, one for which lay juries and state tort law are wholly unsuited. The generic pharmaceutical market is, by congressional design, highly fragmented, with many competitors, any one of whom can possess only a small piece of the overall safety and therapeutic puzzle for a given drug. Only FDA can see the entire picture—

indeed, that is why the agency insists so steadfastly that it, and only it, can dictate the content of a generic product label. In considering whether to adopt a label change, FDA is not limited to information from a single manufacturer in isolation, but rather has access to data from all manufacturers and from wholly independent sources as well, much of which will not be available, or even known, to any single generic manufacturer. FDA may have to consider the potential impact of a proposed label change across an entire therapeutic class, as where there exist multiple brand-name drugs, each with multiple generic equivalents, that present safety or efficacy concerns common to the class. FDA also may have to consider issues that transcend any one drug or even class of drug, as where a change in the manner of use of one drug or class may impact the manner of use of another drug or class.

The hypothetical question of what would FDA do will rarely, if ever, turns solely on factual considerations unique to a single drug product; rather, the inquiry invariably will hinge on broader concerns of FDA regulatory policy. For example, suppose a generic manufacturer were to propose a change to strengthen the suicide warning for its antipsychotic medication. That proposal would affect not only the labeling of the brand-name reference drug and every generic version of that drug, but also every brand-name antipsychotic in the same therapeutic class, together with every generic version of those brands; and the proposal to change the labeling for the antipsychotic class could also impact the labeling of the antidepressant, sedative and anti-anxiety classes as well. In short, a suggested label change for a single drug that may seem entirely reasonable to a lay jury may, in fact, be fundamentally inconsistent with FDA's broader regulatory and public health objectives.

State tort law is well-equipped to resolve factual disputes arising out of particular transactions, events or relationships, but it is ill-suited to answer speculative questions of federal regulatory policy. Indeed, this Court has long held that federal law preempts state-law claims that depend on speculation about what a federal agency would have done in hypothetical regulatory proceedings. *Arkansas La. Gas Co.* v. *Hall*, 453 U.S. 571, 578-79 (1981); see also *Nantahala Power & Light Co.* v. *Thornburg*, 476 U.S. 953, 963-964 (1986); *Chicago & N.W. Transp. Co.* v. *Kalo Brick & Tile Co.*, 450 U.S. 311, 324-27 (1981).

2. Moreover, attempting to adjudicate hypothetical questions of federal healthcare policy under state tort law would impose extraordinary burdens on FDA, and therefore indirectly on the industry and on the public. First, imposition of a state-law duty to "take steps" to prompt FDA to change product labeling inevitably would lead to the agency being inundated with "proposals" from generic manufacturers, driven by the advice of attorneys, not scientists. This is a situation the Court has addressed before, in upholding federal preemption in a similar context, where it observed that such a scheme would:

> cause applicants to fear that their disclosures to the FDA, although deemed appropriate by the Administration, will later be judged insufficient in state court. Applicants would then have an incentive to submit a deluge of information that the Administration neither wants nor needs, resulting in additional burdens on the FDA.

Buckman Co. v. *Plaintiffs' Legal Comm.*, 531 U.S. 341, 351 (2001).

Worse still, most of these proposals inevitably would be counterproductive, since individual generic manufacturers lack access to all the safety data relevant to the drug or class, and thus lack the perspective to appreciate

fully the implications of their requests. The scheme would run up costs for generics, which would be passed on to consumers; would result in a deluge to FDA as a preemptive measure against litigation; and because of the volume and likelihood of irrelevance, would subject FDA to searching for needles in haystacks, diverting resources from the agency's public health mission where they are best used. The current approach, where manufacturers submit incidents as they become aware of them, and FDA evaluates them with the benefit of all the accumulated safety data, avoids each of these ills.

Third, such a scheme would thrust FDA into the middle of private litigation. The pivotal question in every "take steps" trial—what FDA would have done in response to a hypothetical proposal—necessarily would depend on evidence beyond the control of the litigants themselves. To delve into the regulatory mind of FDA, litigants, courts, and juries would require access to the regulatory record and thinking of FDA. The agency, and its documents and personnel, would become the central evidence in every trial. FDA understandably has resisted such intrusion in the past; in 2008, for instance, the United States told this Court:

> In one recent products liability class action, *Walson* v. *Merck & Co.*, No. 3:04-cv-00027-GPM-DGW (S.D. Ill.), FDA devoted approximately 1,300 employee hours to producing approximately 40,000 pages of documents in response to a third-party subpoena. Private litigation such as this would divert FDA's resources and create a substantial potential for distorting its mission.

Br. for the United States as *Amicus Curiae* Supporting Petitioners 7-8, *Warner-Lambert* v. *Kent*, 552 U.S. 440 (2008) (No. 06-1498), 2007 WL 4218889. Even with FDA involvement, the accuracy of any answer to the speculative question is doubtful; without FDA involvement, inac-

curacy would be certain. And depriving the parties of such essential evidence would raise serious due-process concerns—especially under a scheme, such as that proposed here, where the *defendant* would bear the burden of *disproving* the likelihood of FDA action.[22]

Finally, by far the most pernicious consequence of the proposed "take steps" scheme is that it would shift the essential regulatory question—what is a generic manufacturer to do with the information it receives about its drug—from the exclusive province of FDA to the vagaries of fifty varying systems of state tort law. Would a lay jury, guided by a state-law "ordinary care" standard, be allowed to hold a generic manufacturer liable for failing to conduct duplicative clinical testing, notwithstanding FDA's clear and long-standing policy against such a requirement? Or that a generic manufacturer who faithfully collected and reported its safety data to FDA could be liable nonetheless for failing to collect and analyze the safety data of its generic competitors, or even of the brand? Could a jury find that a prudent manufacturer should, as the *Mensing* court suggests, better quit the business altogether than market its drug in the face of regulatory uncertainty?

Indeed, the struggles of the courts below in interpreting and applying FDA labeling regulations only highlight the folly of transferring the regulatory mantel to lay juries guided by state tort law. And the fact that their struggles lead them to concoct a state remedy that is so

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[22] Even were it appropriate for state courts to embark on "take steps" regulatory trials, a notion GPhA vigorously contests, the burden of proof would have to be the reverse of that proposed by the *Mensing* court and the United States. The plaintiff would be required to prove, as part of his or her *prima facie* case, that the defendant manufacturer failed to "take steps" to propose labeling changes that FDA likely would have adopted.

wholly unlike any cause of action traditionally recognized under conventional state tort law is, by itself, sufficient indicia that such a state law claim is inconsistent with the historic police powers of the States and thus preempted by federal law.

The vague injunction to "do something" can easily become, under state tort law, an obligation to do *anything* without regard to its impact on the fundamental Hatch-Waxman goal of "get[ting] generic drugs into the hands of patients at reasonable prices—fast." See *Andrx Pharms.*, 256 F.3d at 809 (internal quotation omitted).[23]

CONCLUSION

The notion that manufacturers of generic drugs may change their product labels without FDA consent is plainly wrong. Federal law forecloses that option. The alternative notion that generic manufacturers can "take steps" to change their labels—the sufficiency of which will be adjudicated piecemeal by lay juries under state tort law, rather than through comprehensive and dispassionate regulation by the federal agency specially charged and equipped for that purpose—is just as plainly wrong. The Court should reverse the judgments below because these questions are preempted by federal law.

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[23] This formulation of the syllogism appeared in a recent article about a different topic: "We must do something; this is something; therefore we must do it." Scrap the Cap, The Economist, Nov. 20, 2010, p. 15. This is no way to manage a healthcare system that is an increasingly substantial part of the national economy. But it is the formula that would govern the proposed "take steps" scheme if the opinions below are affirmed.

Respectfully submitted.

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PLIVA, INC., ET AL., *Petitioners*,
v.
GLADYS MENSING, *Respondent*.

ACTAVIS ELIZABETH LLC, *Petitioner*,
v.
GLADYS MENSING, *Respondent*.

ACTAVIS INC., *Petitioner*,
v.
JULIE DEMAHY, *Respondent*.

On Writs of Certiorari to the United States Courts of Appeals for the Fifth and Eighth Circuits

BRIEF FOR DR. CHRISTY GRAVES AS *AMICUS CURIAE* IN SUPPORT OF RESPONDENTS

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INTEREST OF *AMICUS CURIAE* [1]

Amicus curiae Dr. Christy Graves practices internal medicine in Louisiana and was respondent Julie Demahy's treating physician. Following a diagnosis of gastroesophageal reflux disorder and initial prescription of metoclopramide by Ms. Demahy's gastroenterologist, Dr. Graves continued to prescribe metoclopramide to Ms. Demahy. Because the labeling materials for metoclopramide warned only of a very small risk from the drug of adverse neurological reactions such as extrapyramidal symptoms ("EPS") and tardive dyskinesia ("TD"), Dr. Graves prescribed the drug to Ms. Demahy for approximately four years. Ms. Demahy eventually developed TD. Had Dr. Graves been informed that the product labeling and warnings were grossly inaccurate and that the risk for EPS and TD with long-term use was roughly 100 times higher than stated on the package insert, she would not have prescribed metoclopramide for such an extended period and would have been more alert to the early signs of EPS and TD and sought alternative treatment options.

Dr. Graves is interested in this case because of her personal experience with the harm that inadequate drug label warnings caused for one of her own patients, her direct knowledge of how misleading warnings can affect treatment decisions and lead to treat-

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[1] No counsel for a party authored this brief in whole or in part, nor did any person or entity, other than *amicus* or her counsel, make a monetary contribution intended to fund the preparation or submission of this brief. This brief is submitted pursuant to the blanket consent letters from all parties, on file with this Court.

ment choices having far worse risk-benefit profiles than expected, and her desire to ensure that doctors now and in the future have accurate and current information in the drug labeling on which they rely when making treatment decisions.

STATEMENT

In attempting to avoid responsibility for the content of their drug labels, the generic manufacturer petitioners in these cases argue that updating the warnings contained in the labels is the sole responsibility of the brand-name manufacturer and that they are only required to match the labeling of that manufacturer, not seek updates on their own. Actavis Br. at 7, 16, 19-20; PLIVA Br. at 12-13, 37-38.

They claim variously that requiring generic manufacturers to monitor the market and medical evidence for adverse effects from their drugs and alert the FDA to emergent risks is too costly and burdensome for them, is beyond their competence, and would impose a burden on the FDA. Actavis Br. at 20 n. 13, PLIVA Br. at 4, 30, 37-38.

Each of those claims is undermined by the history of metoclopramide, the extensive medical evidence that emerged during the 1980s and 1990s regarding the higher-than-warned risks of neurological side-effects associated with metoclopramide use, and the FDA's eventual and late-coming unilateral actions to strengthen the warnings for metoclopramide once it became aware of such evidence.

SUMMARY OF ARGUMENT

From 1985 through 2009, the warnings in the labeling for metoclopramide asserted that it carried a low risk – only 0.2% or 1 in 500 – of a class of neurological side effects called extrapyramidal symptoms ("EPS"), including a severe side-effect called tardive dyskinesia ("TD"). Extensive evidence in the medical literature, however, showed that warning to be a gross underestimate. The actual risk of EPS and TD, particularly with long-term use of metoclopramide, was in fact at least 100 times higher.

Such information was readily available to generic manufacturers through published medical reports and studies and through the FDA's publicly available database of reported adverse drug reactions. No extensive studies were required; no post-market clinical testing, and no pre-existing experience with clinical trials from before metoclopramide was approved. All the generic manufacturers needed to do was monitor the medical literature for articles on their own drug and periodically check the FDA database for new reports relating to metoclopramide.

Had the generic manufacturers taken those steps they readily would have found and easily understood the evidence described in this brief and been able to take appropriate action – whether attempting to issue a non-misleading warning or requesting from the FDA a strengthened warning for all metoclopramide labels. Such minimal efforts are a far cry from the purported difficulties petitioners claim attend post-market monitoring, would not have meaningfully added to the costs of generic metoclopramide, would have averted untold suffering among patients, and

likely would have lowered the overall cost of health care by avoiding the medical and legal costs of metoclopramide-induced EPS and TD.

The readily available evidence of a higher risk of EPS and TD from metoclopramide has several implications for the preemption theories asserted by petitioners. At a minimum it demonstrates that the post-market monitoring needed to remain abreast of the heightened risks of metoclopramide-induced EPS and TD was fairly straight-forward and not unduly burdensome. Satisfying their state-law duty to warn thus would not conflict with the various other goals of federal law and policy regarding generics, and in fact would be consistent with the more fundamental federal concern regarding accurate safety information in drug labeling. The history demonstrates that generic manufacturers were not incapable of monitoring post-market safety information, and cannot simply pass the buck to the brand manufacturer by claiming a lack of expertise or context.

The FDA's response to the evidence of heightened risks from metoclopramide also undermines petitioners' claims that this case requires an intrusive inquiry into the FDA's decision-making processes or that it requires impermissible second-guessing and speculation. When the FDA finally considered the evidence of metoclopramide-induced TD in 2008-2009, it acted decisively and urgently to add a black-box warning to the product. It did so based on much of the same information that had been available for more than a decade. There is little need to speculate regarding the FDA's reaction to that same information had generic manufacturers submitted it earlier

in connection with a proposed labeling change. The suits in these cases thus pose no threat to the FDA or federal law and complement, rather than obstruct, their functions.

ARGUMENT

I. The High Risk of Metoclopramide-Induced EPS and TD Was Readily Discoverable by Generic Manufacturers Long Before the FDA Added a Black-Box Warning.

As described in Respondents' Brief, at 6, metoclopramide or Reglan® is a drug approved for short-term use in treating recurrent diabetic gastric stress and gastric reflux. It is a dopamine antagonist – blocking the dopamine receptors that receive signals between nerves. *Id.* Like other drugs of its class, it can have adverse effects on the body's nervous system, in particular the body's extrapyramidal system, which controls fine motor movement. Such adverse neurological effects are known as extrapyramidal symptoms ("EPS") and involve a loss of control over various fine motor movements. A particularly severe form of EPS is tardive dyskinesia ("TD"), which involves "grotesque involuntary movements of the mouth, tongue, lips, and extremities, involuntary chewing movements, and a general sense of agitation." *McNeil* v. *Wyeth*, 462 F.3d 364, 366 (CA5 2006).

Metoclopramide was originally approved by the FDA in 1980 and sold under the brand name Reglan®. *Mensing* v. *Wyeth, Inc.*, 588 F.3d 603, 606 (CA8 2009). Generic versions of metoclopramide began receiving FDA approval in 1985. *Id.* The ap-

proved uses for metoclopramide were for relatively short durations – between 2 and 12 weeks. Resp. Br. at 6 (citing Reglan label published in the Physician's Desk Reference from the early to mid-1980s).

Since 1985 and throughout the time period relevant to this case, the labeling for branded and generic metoclopramide advised of a low risk of EPS of all kinds – only 1 in 500, or 0.2%. Resp. Br. at 7-8 (quoting label warnings). The incidence of TD was not separately described on the label, but because it is a mere subset of EPS, the label necessarily suggested an even lower incidence of TD than of EPS generally.

By 2001 and 2002, however, when respondents began taking generic metoclopramide, it was well known that the drug was routinely prescribed for longer periods than the label suggested.[2] And, during the more than 20 years between the initial approval of metoclopramide and when respondents began taking it, a substantial quantity of publicly available evidence accumulated that the risks of EPS and TD were much higher than claimed on the label.

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[2] Resp. Br. at 7; Robert B. Stewart, James J. Cerda, Mary T. Moore & William E. Hale, *Metoclopramide: An Analysis of Inappropriate Long-Term Use in the Elderly*, 26 ANN. OF PHARMACOTHERAPY 977, 978 (July/Aug. 1992) ("long-term treatment with [metoclopramide] has become more common"); P. Jay Pasricha, Nonko Pehlivanov, Aravind Sugumar & Joseph Jankovic, *Drug Insight: from disturbed motility to disordered movement – a review of the clinical benefits and medicolegal risks of metoclopramide*, 3 NATURE CLINICAL PRACTICE GASTROENTEROLOGY & HEPATOLOGY 138, 141 (March 2006) ("Despite the recommendation for short-term use (4-12 weeks), metoclopramide is frequently prescribed for chronic use.").

In 1989, for example, a published review of 16 cases of metoclopramide-related movement disorders, noted that there were "[a]t least 1031 patients with metoclopramide-induced movement disorders" described in the medical literature. Lucinda G. Miller & Joseph Jankovic, *Metoclopromide-Induced Movement Disorders*, 149 ARCH. INTERN. MED. 2486, 2489 (Nov. 1989). The authors observed that "[d]espite the manufacturer's estimate of only 0.2% frequency of metoclopramide-induced movement disorders, the actual prevalence is probably greater." *Id.* (footnote omitted)

In 1992, another published analysis noted the increased long-term use of metoclopramide and the resulting increased incidence of TD. Robert B. Stewart, James J. Cerda, Mary T. Moore & William E. Hale, *Metoclopramide: An Analysis of Inappropriate Long-Term Use in the Elderly*, 26 ANN. OF PHARMACOTHERAPY 977, 978 (July/Aug. 1992) ("TD originally was thought to be a very rare adverse effect of metoclopramide treatment, particularly as the drug is usually intended for short-term therapy. However, as long-term treatment with this drug has become more common, the incidence of TD has increased.") (footnote omitted).

In 1993, researchers set out to quantify the incidence of EPS and TD caused by metoclopramide. They initially observed that merely looking to the incidence reports filed with the FDA was inadequate because many adverse reactions are simply not reported. Linda Ganzini, Daniel E. Casey, William F. Hoffman & Anthony McCall, *The Prevalence of Metoclopramide-Induced Tardive Dyskinesia and Acute*

Extrapyramidal Movement Disorders, 153 ARCH. INTERN. MED. 1469, 1471 (June 28, 1993) ("adverse drug reaction registries underestimate the true incidence of EPS because of substantial underreporting.[]") (footnote omitted). Such underreporting and the lack of studies on the true rate of metoclopramide-induced TD was a problem in their view:

> Despite the absence of prevalence studies, the manufacturer's product labeling reports the incidence of all metoclopramide-induced EPS at 0.2%.[] Our clinical experience suggests that the true prevalence of metoclopramide-induced EPS is substantially higher than reported by the manufacturer.

Id. (footnote omitted).

To remedy the deficiency in the data on metoclopramide-induced EPS, the authors thus conducted their own controlled prevalence study of patients taking metoclopramide. That study found that 29% of patients taking metoclopramide had TD as compared to 17% of the control group. *Id.* at 1472. The incidence of another EPS – parkinsonism – was likewise considerably higher for patients taking metoclopramide: 31% as compared to 7.8% for the control group. *Id.* at 1473; *see also id.* (the "results indicate that the prevalence and severity of EPS, including tardive dyskinesia, drug-induced parkinsonism, and subjective akathasia, were significantly increased in a group of chronically ill, older, metoclopramide-treated men").

The authors raised as plain a red-flag as can be imagined, concluding that their "data clearly suggest that both the prevalence and severity of metoclopra-

mide-induced acute EPS and tardive dyskinesia have been underestimated and underrecognized and are approximately *100 times more prevalent than previously reported.*" *Id.* (emphasis added).

Another controlled study published by a different group of researchers in 1994 reached similar conclusions, finding that the incidence of TD in metoclopramide-treated patients was 27%, as compared to 12% in the control group. Daniel D. Sewell, Angela B. Kodsi, Michael P. Caligiuri & Dilip V. Jeste, *Metoclopramide and Tardive Dyskinesia*, 36 BIOL. PSYCHIATRY 630, 631 (1994).

These studies and the numerous published reports of metoclopramide-induced EPS and TD cited by the authors were more than enough to raise serious concerns that the labeling for metoclopramide was inaccurate and misleading.

Indeed, in a review of the literature twelve years later, the Ganzini and Sewell studies continued to be cited as evidence that EPS "probably occur more frequently than is realized." P. Jay Pasricha, Nonko Pehlivanov, Aravind Sugumar & Joseph Jankovic, *Drug Insight: from disturbed motility to disordered movement – a review of the clinical benefits and medicolegal risks of metoclopramide*, 3 NATURE CLINICAL PRACTICE GASTROENTEROLOGY & HEPATOLOGY 138, 143-44 (March 2006).

The Pasricha review also discussed a further source of information that was readily available to generic metoclopramide manufacturers throughout the period relevant to this case: the FDA's database of reported adverse drug reactions, the Adverse Event Reporting System or 'AERS." "Between 1968 and

2003, the Adverse Event Reporting System database of the medwatch program maintained by the FDA contained 87 cases of tardive dyskinesia" in patients taking metoclopramide *Id.* at 142. "Permanent disability was reported in nearly 25% of cases." *Id.* at 143; *see also* Douglas Shaffer, Marian Butterfield, Carol Pamer & Ann Corken Mackey, *Tardive Dyskinesia Risks and Metoclopramide Use Before and After U.S. Market Withdrawal of Cisapride*, 44 J. AM. PHARM. ASS'N 661, 663 (Nov./Dec. 2004) (noting at least 87 cases of metoclopramide-associated tardive dyskinesia reported to AERS prior to mid-2003, most involving long-term use of the product).

Having reviewed both published reports and AERS information that was equally available to generic manufacturers, the Pasricha article described the 0.2% EPS frequency estimate as "probably a gross underestimation" due to the likely failure to include the elderly in the prospective clinical trials, difficulty recognizing the early signs of EPS, and the short length of the studies compared with the longer exposure likely to trigger EPS. Pasricha, *et al.*, 3 NATURE CLINICAL PRACTICE GASTROENTEROLOGY & HEPATOLOGY at 143. And the authors noted the "consistent finding * * * that elderly women are at the highest risk of developing tardive dyskinesia." *Id.*

Despite the readily available evidence of greater risks from metoclopramide than disclosed in the labeling, there is no evidence than any of the petitioners informed the FDA of the inadequacy of the labeling or sought to strengthen the warnings.

Indeed, it was not until 2009 that the FDA, on its own initiative took action to strengthen the warnings

for metoclopramide. As the Eighth Circuit described below in *Mensing*: "Acting on its own initiative pursuant to the Food and Drug Administration Amendments Act of 2007, Pub.L. No. 110-85, 121 Stat. 823 (FDAAA), the FDA ordered manufacturers of Reglan and generic metoclopramide on February 26, 2009 to add a boxed warning to their labels about the increased risks of tardive dyskinesia from long term metoclopramide usage." 588 F.3d at 607.

In FDA's 2008 internal report describing its reasons for adding stronger warnings for metoclopramide, the FDA cited the 1993 Ganzini study as well as the review of the literature by Pasricha, *et al.*, described above, both of which noted a higher incidence of TD than disclosed in the product labling. Memorandum from Kate Gelperin, *et al.*, Office of Surveillance and Epidemiology, CDER, FDA, to Donna Griebel, Director, Division of Gastroenterology Products, OND, CDER, FDA, *Risk of Metoclopramide-induced Movement Disorders*, June 27, 2008, at 5 (OSE RCM # 2008-269) ("Gelperin Report"). The report also noted two other studies looking at patients with movement disorders or taking drugs for Parkinson's or similar conditions and noted the high percentage of such patients that had a high rate of previous metoclopramide use, suggesting that a substantial percentage of EPS and TD cases were being caused by metoclopramide. *Id.* at 6.

In addition, the FDA identified 80 adverse event reports between 2001 and 2008 in its AERS database involving metoclopramide-associated TD. *Id.* 9. And it noted the article by Shaffer, *et al.*, identifying 87 cases of metoclopramide related TD through 2003.

Id. at 10. The report recognized that the AERS data likely underrepresented the occurrence of TD due to underreporting. *Id.*

In its discussion section, the FDA report noted that its review of the literature suggested that "the risks would appear to outweigh the clinical benefit of metoclopramide in chronic conditions such as GERD [gastroesophageal reflux disease] where effective drug therapies with better safety profiles are available." *Id.* at 13. It concluded that "[f]rom a regulatory and public health perspective, heightened awareness of the risk of movement disorders with metoclopramide use is urgently needed." *Id.* at 14.

The report recommended a boxed warning – the strongest type available – as well as a public health advisory in order to emphasize the dangers of long-term metoclopramide use. *Id.* at 14. The resulting 2009 warnings required by the FDA significantly strengthened the label discussion of TD and noted the 100-times greater risk identified in the literature. The boxed warning itself stated, *inter alia*, that

> Chronic treatment with metoclopramide can cause tardive dyskinesia, a serious movement disorder that is often irreversible. The risk of developing tardive dyskinesia increases with the duration of treatment and the total cumulative dose. The elderly, especially elderly women, are most likely to develop this condition. * * *. Prolonged treatment (greater than 12 weeks) with metoclopramide should be avoided in all but rare cases where therapeutic benefit is thought to outweigh the risks to the patient of developing tardive dyskinesia.

See Letter from Joyce Korvick, Deputy Dir. for Safety, Div. of Gastroenterology Products, Center for Drug Evaluation and Research (CDER), FDA, to NDA holders for Reglan, 2 (Feb. 26, 2009).[3] The required revision to the Warnings section of the label identified the much higher incidence of TD when used long-term and the greater risk to elderly women, stating:

> Although the risk of tardive dyskinesia (TD) with metoclopramide has not been extensively studied, one published study reported a TD prevalence of 20% among patients treated for at least 3 months.
>
> The prevalence of the syndrome appears to be highest among the elderly, especially elderly women. It is impossible to predict which patients are likely to develop the syndrome. Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase with the duration of treatment and the total cumulative dose.

Id. at 3.

What is most notable about the FDA's action is that it was based on information that had been available for years, yet had not been adequately brought to the FDA's attention by petitioners or others. Indeed, the TD incidence data cited by FDA was the same 1992 Ganzini study discussed above and the 2006 Pasricha review of the literature citing that same study and another from 1993. All of that information and

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[3] The letter requiring the change can be found online at http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM111376.pdf.

more easily could have been identified by petitioners in these cases and brought to the FDA's attention more than a decade earlier and well before respondents began taking metoclopramide.

The failure to revise the warnings for metoclopramide earlier is especially tragic given the limited medical benefits of the drug and hence the importance to doctors of accurate risk information in determining whether the limited benefits are worth the risks. In reviewing the literature on metoclopramide, Pasricha, *et al.*, noted that "the drug is seldom capable of producing dramatic clinical improvement when administered chronically." Pasricha, *et al.*, 3 NATURE CLINICAL PRACTICE GASTROENTEROLOGY & HEPATOLOGY at 145. He further observed that "[i]n many cases, an alternative drug or a shorter duration of treatment could probably have adequately controlled the gastrointestinal symptom." *Id.* at 141. Indeed, due to the high risks and limited utility of metoclopramide, the American Gastroenterological Association gave metoclopramide a grade of "D" (on the A, B, C, D scale) for use in treatment of GERD, recommending against its use based on "fair evidence that it is ineffective or harms outweigh benefits." American Gastroenterological Ass'n Institute, *American Gastroenterological Association Medical Position Statement on the Management of Gastroesophageal Reflux Disease*, 135 GASTROENTEROLOGY 1383, 1384 (2008).

II. The History of Inaction in the Face of Readily Available Evidence of Metoclopramide's Risks Counsels Against Preemption.

The fact that substantial evidence of the risks of metoclopramide-induced EPS and TD was publicly available for nearly two decades before the FDA was forced to unilaterally act on that information strongly counsels against preemption in this case. Generic manufacturers have a state-law duty to warn their customers of the genuine risks of their products, and the label for metoclopramide was woefully inadequate for decades. Respondents are not required by federal law to sit idly by in the face of evidence that their labels are misleading, and should not be given a free pass by claiming that providing accurate safety information is too burdensome for them and is the exclusive obligation of the brand-name manufacturer.

Review of publicly available information is not unduly burdensome. As the previous section demonstrates, the evidence of EPS and TD from long-term metoclopramide was readily and publicly available and would have been relatively simple for generic manufacturers to discover and analyze. Such evidence more than amply signaled that a stronger warning was necessary and that the existing warning was inadequate. Indeed, the evidence easily satisfies the requirement that a drug's "labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved." 21 C.F.R. § 201.80(e).

Contrary to the assertions by petitioners, PLIVA Br. at 37-38, such analysis would not have been par-

ticularly difficult, required no burdensome clinical studies, required no extensive knowledge of prior clinical studies performed by the brand manufacturer, and would have raised numerous red flags regarding EPS and TD. Articles in the medical literature were quite explicit in drawing the obvious and indisputable conclusion that the risks reported on the labeling were grossly understated. *See* Ganzini, *et al.*, 153 ARCH. INTERN. MED. at 1471, 1473 ("the true prevalence of metoclopramide-induced EPS is substantially higher than reported by the manufacturer"; "both the prevalence and severity of metoclopramide-induced acute EPS and tardive dyskinesia have been underestimated and underrecognized and are approximately 100 times more prevalent than previously reported"); Pasricha, *et al.*, 3 NATURE CLINICAL PRACTICE GASTROENTEROLOGY & HEPATOLOGY at 143, 145 (0.2% EPS frequency estimate as "probably a gross underestimation"; "the risk of developing tardive dyskinesia seems to be grossly underestimated in the package insert").[4]

The FDA's publicly available AERS database likewise contained publicly available information that

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[4] Tellingly and tragically, it was the failure of manufacturers to do even the most basic review of the scientific literature that was one of the factors in the 1937 Sulfanilamide disaster. *See* Carol Ballentine, *Taste of Raspberries, Taste of Death: The 1937 Elixir Sulfanilamide Incident*, FDA CONSUMER (June 1981) (http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/SulfanilamideDisaster/default.htm) ("Even a review of the current existing scientific literature would have shown that other studies--such as those reported in several medical journals--had indicated that diethylene glycol was toxic and could cause kidney damage or failure."). That disaster, of course, led to the adoption of the FDCA.

required no extraordinary measures to access and analyze. Had respondents merely reviewed the reports in AERS, it would have discovered 87 instances of metoclopramide-related EPS through 2003. That number certainly would have raised a red flag, and is far more than the 20 adverse events noted by this court in *Wyeth* v. *Levine*, -- U.S. --, 129 S. Ct. 1187, 1193 (2009).

Petitioners' claim that generic manufacturers receive only limited numbers of adverse event reports and hence cannot place them in context, PLIVA Br. at 38, gets it only half right. While it is true that few adverse event reports are submitted directly to the generic manufacturers, it is simply not true that they are incapable of putting such reports in context. All respondents had to do was look to the database itself and *read* the other reports, regardless of who submitted them. Despite any imbalance in the source of reports to the AERS database, there is no imbalance whatsoever in access to all the reports. The only reason generic manufacturers would lack context for their reports would be if they simply refused even to look at the other reports on the database. The notion that generic manufacturers would turn such a blind eye to the consequences of the drug they sell, feigning ignorance and relying on the brand manufacturers to do their work for them, is precisely why it is important to have state law tort remedies.

The subsequent FDA response to evidence regarding EPS and TD obviates causation concerns. As described in Part I, the evidence available to respondents for years was largely the same evidence relied upon by FDA more than a decade later when it finally

considered the issue and in 2009 ordered a black-box warning concerning the risks of EPS and TD from long-term metoclopramide use. Given the FDA's actual response to such evidence, there is no need to speculate about what it would have done if the generic manufacturers had raised the same evidence and concerns earlier. FDA would have done *what it in fact did* – add a warning.

Petitioners' reliance on *Buckman Co.* v. *Plaintiffs' Legal Comm.*, 531 U.S. 341 (2000), is inapposite, particularly in light of the actual history of metoclopramide. Given FDA's "explicit actions" in response to the same information petitioners should have provided earlier, there is no need for "speculation as to the FDA's behavior in a counterfactual situation" and no need for "second guessing the FDA's decisionmaking or overburdening its personnel." *Id.* at 354 (Stevens, J., joined by Thomas, J., concurring in the judgment). Because we already know the FDA's response to the late-acquired, but long-available, evidence of higher EPS and TD rates than disclosed on the label, this is indeed a "different case" than *Buckman* and does not raise the same type of concerns underlying *Buckman*. *Id.*

This case is instead more comparable to *Wyeth* v. *Levine*, where this Court viewed state-law failure-to-warn suits as "complementary," rather than antagonistic, to FDA's mission. -- U.S. at --, 129 S. Ct. at 1202. Indeed, far from discouraging generic manufacturers from bringing safety concerns to its attention, FDA regulations in fact *require* manufacturers to report on such concerns. *See* 21 C.F.R. § 314.80(b) (requiring manufacturers to "promptly review all ad-

verse drug experience information obtained or otherwise received by the applicant from any source, foreign or domestic, including information received from * * * postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers" and submit reports and follow-up information to the FDA). And FDA regulations provide that a drug whose label lacks an adequate warning of a serious risk is misbranded. *See* 21 U.S.C. § 352(f)(2); 21 C.F.R. § 201.57(e) That obligation squarely rebuts the notion that FDA will be burdened with *unwanted* safety information and concerns as a result of state-law duties to warn. Rather, the FDA has an interest, if not an affirmative duty, to address misbranded drugs. And the history of metoclopramide reflects that the FDA in fact acts on that interest, subject to its inherent limitations. Indeed, earlier efforts to improve the warnings on metoclopramide would undoubtedly been welcomed by the FDA. When the FDA finally got to the issue of long-term use of metoclopramide on its own, it concluded that "heightened awareness of the risk of movement disorders with metoclopramide use is urgently needed." Gelperin Report at 14.

As in *Wyeth*, state law incentives to keep safety information in product labels current and accurate constitute "an additional, and important, layer of consumer protection that complements FDA regulation" and supplements FDA's "limited resources to monitor the 11,000 drugs on the market." -- U.S. at --, 129 S. Ct. at 1202. Ultimately, however, grounding preemption on uncertain concerns over how FDA will handle increased information and efforts by generic

manufacturers to keep their labels current and accurate, or what effect it will have on the cost of generic drugs, is a poor basis for preemption. Those concerns are not founded on any direct conflict with statutory or regulatory provisions, but rather an amorphous notion of "obstacle" preemption based on overly simplified views of the objects and purposes of federal law. But, as Justice Thomas has noted, federal law rarely has a single purpose, and elevating one purpose above the other is not a proper basis for preempting state law. *Wyeth*, -- U.S. at --, 129 S. Ct. at 1215-17 (Thomas, J., concurring in the judgment).

Petitioners would have this Court elevate cost and convenience above safety as the sole "object" of federal law regarding generic drugs. But federal law seeks to advance both goals, and conspicuously lacks an express preemption provision. Petitioners' efforts to preempt state law based on their – or this Court's – view as to which goal is more important and whether state-law claims might be an obstacle to that goal improperly invade the States' traditional authority over health and safety and should be rejected.

CONCLUSION

For the reasons above, this Court should affirm the decisions below.

Respectfully submitted,

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In the Supreme Court of the United States

PLIVA, INC., *et al.*, *Petitioners*,
v.
GLADYS MENSING, *Respondent*.

ACTAVIS ELIZABETH, LLC, *Petitioner*,
v.
GLADYS MENSING, *Respondent*.

ACTAVIS INC., *Petitioner*,
v.
JULIE DEMAHY, *Respondent*.

On Writs of *Certiorari* to the United States Courts of Appeals for the Eighth and Fifth Circuits

BRIEF OF JEROME P. KASSIRER, M.D., AND PAUL D. STOLLEY, M.D., M.P.H., AS *AMICI CURIAE* FOR RESPONDENTS

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QUESTION PRESENTED

Does the Drug Price Competition and Patent Term Restoration Act of 1984 ["Hatch-Waxman Act"][1] preempt state-law failure-to-warn claims against manufacturers of generic drugs?

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[1]Pub. L. No. 98-417, 98 Stat. 1585 (1984); *see* 21 U.S.C. §156 and 35 U.S.C. §271.

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INTEREST OF *AMICI CURIAE*

Amici Curiae are distinguished physicians and academicians with decades of experience in public health and drug safety.

Amicus Jerome P. Kassirer, M.D., Distinguished Professor at Tufts University School of Medicine, served as *New England Journal of Medicine's* ["NEJM"] Editor-in-Chief between 1991 and 1999, after which he was named Editor-in-Chief Emeritus. NEJM is the oldest continuously published medical journal in the world and one of the most respected. During his tenure at NEJM, it published numerous scholarly articles on prescription drug side effects and the respective roles of the U.S. Food and Drug Administration ["FDA"] and pharmaceutical industry in the nation's health care system.

Amicus Paul D. Stolley, M.D., M.P.H., has spent 40 years working in the fields of epidemiology and public health with a special focus on adverse drug reactions and how to prevent them. He is a faculty member of the Johns Hopkins School of Public Health, The University of Pennsylvania School of Medicine, and Chairman of the Department of Epidemiology and Public Health at the University of Maryland School of Medicine. Dr. Stolley has served on many advisory committees, most dealing with drug safety, for FDA, National Institutes of Health ["NIH"], and the National Academy of Science's Institute of Medicine ["IOM"], where he is an elected Member. In particular, Dr. Stolley spent a sabbatical year at FDA as consultant to its Drug Safety Division. He also served as President of the Society for Epidemiologic Research and the American Epidemiologic Society. An NEJM Editorial Board member from 1989-1993, Dr. Stolley

has published over 200 articles and 30 book chapters, including 15 in NEJM, many dealing with the epidemiology of adverse drug reactions, drug regulation, and surveillance and prevention of drug reactions. He is also co-author of three books in the field of epidemiology.

The question presented to this Court – whether federal law preempts failure-to-warn claims relating to generic drugs – is one of great significance to public health and safety. It also falls directly within *amici's* professional expertise and responsibility to ensure that prescription drugs best serve the cause of public health. To that end, *amici* are compelled to file this brief. They ask this Court to affirm the decisions below.

SUMMARY OF ARGUMENT

The safety profile of prescription drugs – what their side effects might be and the likelihood of their occurrence – is not static. Instead, as drugs are prescribed for more and varied patients, studied by doctors and scientists, evaluated for new indications, and reevaluated for traditional ones, sometimes over decades, their safety profiles evolve. Once cheered as a "wonder drug" for morning sickness in Europe, Thalidomide was subsequently banned in the United States when it was found to cause severe birth defects. Decades later, it reemerged as a cancer treatment. The establishment of a drug's safety profile is, therefore, an ongoing, organic process, a fact FDA and NIH concede.

Equally important, this evolution often takes time. One study found that "many serious ADRs [adverse drug reactions] are discovered only after a drug has been on the market for years. Only half of newly discovered serious ADRs are detected and documented

in the Physicians' Desk Reference within 7 years after drug approval."[2]

Petitioners and their industry amici, however, ask this Court to immunize them from state failure-to-warn lawsuits based on the false assumption that safety profiles of *generic* drugs are definitively established upon FDA approval. They argue that, because generic drug manufacturers need not conduct clinical trials before their drugs may be marketed in the United States, brand-name manufacturers' pre-approval studies suffice to "validate the generic product's safety..." Brief of Petitioners Pliva, Inc., *et al.*, at 11. They, therefore, ask this Court to free them from responsibility for revising or seeking revisions to their labeling, or otherwise informing doctors and patients when new or more serious side effects associated with their drugs emerge because the safety profiles of FDA-approved generic drugs are definitely established unless and until FDA alone changes them.

In *Wyeth v. Levine*, 129 S. Ct. 1187, 1210 (2009), this Court rejected the notion that safety profiles of new drugs are conclusively established when they are approved by FDA. Both FDA and NIH recognize the inherent and practical limitations of pre-approval clinical trials in assessing drug safety and the need for ongoing, post-marketing monitoring of a drug's safety over its market life.

These considerations only grow in importance when FDA approves generic equivalents. Federal law authorizes their approval when brand-name drugs' legal protections end, not because their safety profile

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[2]Karen Lasser, *et al.*, *Timing of New Black Box Warnings and Withdrawals for Prescription Medication*, 287 JAMA 2215, 2218 (May 1, 2002).

has been definitively established. In fact, because the time between FDA approval of a new drug and its generic equivalent is often as short as four years, it is unlikely that a drug's safety profile will have time to emerge before generics are marketed.

Instead, as the case of metoclopramide [Reglan] demonstrates, many widely-used prescription drugs have been withdrawn or had their use severely restricted when serious side effects were identified decades after FDA first approved their use. In the case of promethazine [Phenergan], its true dangers were not revealed until more than 50 years after approval and years after generic equivalents were approved.

The battle over suicide warnings for selective seratonin reuptake inhibitor ["SSRI"] antidepressants began shortly after Prozac [fluoxetine] was approved. It lasted twenty years, long after generic SSRI equivalents had flooded the market. With gabapentin [Neurontin], an anti-epilepsy drug, FDA and the medical community were misled about its suicide risks for years by its manufacturer's public denials and illegal promotion of wide-ranging, off-label use. In the mean time, generic equivalents competed for the expanded market.

Finally, the story of isotretinoin [Accutane] shows how information about devastating side effects can be hidden from the medical community, regulators, and patients for years behind inadequate warnings. These histories starkly illustrate the Herculean task FDA *already* faces in attempting to ensure the safety of prescription drugs. Petitioners would increase that burden exponentially by making FDA the sole arbiter of drug safety.

By any objective measure, FDA lacks adequate information, resources, and authority to protect the

public against pharmaceutical risks. In fact, FDA concedes that its post-marketing responsibilities have outstripped the resources and authority available to address them. In desperation, it has resorted to regulatory triage, marshaling its limited resources to address only high-risks.

This untenable situation – that will worsen if Petitioners succeed here – has not been remedied by passage of the Food and Drug Administration Amendments Act ["FDAAA"], Pub. L. 110-85, 121 Stat. 823 (2007). It does not empower FDA to act unilaterally or immediately; therefore, it does not remedy the problems three comprehensive studies identified.

Finally, while FDA's proposed data-mining programs might assist it in post-marketing monitoring some day, technical and financial limitations, privacy, and constitutional concerns cast doubt on FDA's ability to implement them in the foreseeable future.

For these and the reasons that follow, the decisions of the courts below should be affirmed.

ARGUMENT

I. A PRESCRIPTION DRUG'S SAFETY PROFILE IS NOT DEFINITIVELY ESTABLISHED BECAUSE FDA APPROVES ITS MARKETING IN GENERIC FORM

In their briefs, Petitioners and industry amici stress that generic drug manufacturers need not conduct clinical trials themselves but may rely instead on brand-name manufacturers' pre-approval studies "to validate the generic product's safety ..." Pliva Brief, *supra*, at 11. In making this argument, they assume

that the safety profiles of *both* drugs have been definitively established by FDA approval of their marketing and labeling. As demonstrated below, even FDA concedes that they have not.

A. A Brand-Name Prescription Drug's Safety Profile is Not Definitively Established Because FDA Approves the Drug

No prescription drug may be sold in interstate commerce without FDA approval. 21 U.S.C. §§301, *et seq.* (2006). When FDA approves a drug, however, it does not categorically declare that drug safe for all uses and all populations. As Justice Breyer explained in *Levine*, 129 S. Ct. at 1210 (Breyer, J., concurring), FDA approval "does not represent a finding that the drug, as labeled, can never be deemed unsafe by later federal action ... the application of state law," or evolving science.

Instead, FDA approval simply means that a prescription drug has overcome two regulatory hurdles: first, FDA has approved an Investigational New Drug Application ["INDA"] for specific indications and authorized its manufacturer to begin clinical trials; second, after successful completion of clinical trials, FDA has approved a New Drug Application ["NDA"] for the drug, which includes data from the clinical trials, and has allowed the drug to be marketed in the United States for specified indications and populations. 21 U.S.C. §355(c)(1), (d) (2008).

Even FDA's own performance reports acknowledge the inherent limitations of pre-approval studies in identifying drug risks. Clinical trials typically study only a few hundred to, at most, 3,000 patients for 6 weeks to 2 years. "The relatively small size required to

make pre-marketing clinical trials practical means that CDER [FDA's Center for Drug Evaluation and Research] cannot learn everything about the safety of a drug before its approval. As a result, a degree of uncertainty always exists about the risks of drugs."[3] These limitations include samples that are too small to show statistically-significant but catastrophic side effects or trials too short in duration to reveal side effects that develop over time.

Moreover, clinical trials study drugs only in connection with indications specified in the INDA/NDA. They cannot study "off-label" uses that develop years after approval. "Off-label" use means prescribing a drug for indications or populations that have *not* been FDA-approved – or evaluated during clinical trials. Off-label use is particularly attractive to manufacturers because it costs little compared to the expense of filing an NDA for a new indication.

The practice is legal and ubiquitous. *Seventy-four percent* of prescriptions for anti-convulsants [like Neurontin] and *sixty percent* for anti-psychotics are for use off-label.[4] The number of these prescriptions for

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[3] FDA, *FY 2009 Performance Report to the President and Congress for the Prescription Drug User Fee Act* (2010), at 106 ["FY 2009 Report"], *available at* http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/PDUFA/ucm228020.htm.

[4] Randall Stafford, *Regulating Off-Label Use – Rethinking the Role of the FDA*, 358 NEW. ENG. J. MED. 1427, 1428 (2008). Anti-psychotics are the biggest selling drugs in America by therapeutic class, generating $14.6 billion in sales in 2008, according to industry sources. IMS Servs., *2008 U.S. Sales and Prescription Information*, http://www.imshealth.com/portal/site/imshealth/menuitem.a46c6d4df3db4b3d88f611019418c22a/?vgnextoid=85f4a56216a10210VgnVCM100000ed152ca2RCRD&cpse

children and adolescents doubled to 4.4 million between 2003 and 2006, even though no anti-psychotic, brand-name or generic, had ever been FDA-approved for pediatric use at the time. Thus, for vast segments of the pharmaceutical market, clinical trials are irrelevant to drug safety.

Finally, women, minorities, and the elderly have long been significantly under-represented in clinical trials.[5] If studies do not reflect the patient population,

> unforeseen safety problems may become apparent after the drug is already marketed, possibly resulting in increased morbidity and mortality for certain patients. This proved to be the case at the end of the 1990's, when eight in ten of the prescription drugs pulled from market were found to pose greater health risks for women than men.

Id. at 9. The under-representation of the elderly in clinical trials is even more pronounced, even in trials addressing diseases associated with aging such as Alzheimer's.[6]

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[5] Baylor College of Medicine, Chronic Disease Prevention and Control Research Center, EDICT Project, *Major Deficiencies in the Design and Funding of Clinical Trials: A Report to the Nation on Improving How Human Studies are Conducted* 3 (Apr. 1, 2008), *available at* http://www.bcm.edu/edict/PDF/EDICT_Project_White_Paper.pdf

[6] *See, e.g.*, Jiska Cohen-Mansfield, *Recruitment Rates in Gerontological Research: The Situation for Drug Trials in Dementia May Be Worse Than Previously Reported*, 16 ALZHEIMER DIS. & ASSOC. DISORDERS 279, 279-80 (2002)

While NIH mandates that these groups be proportionately represented as subjects of federally-funded clinical research, most clinical trials still fall well short of inclusion targets and the situation is not improving. *See* Baylor College of Medicine, *supra* note 6, at 21. Worse, because FDA views NIH as the sole agency responsible for addressing disparities in clinical trials, FDA *does not evaluate* whether clinical trials include women or other under-represented populations. *Id.* This omission raises the real possibility that safety data generated in clinical trials will not provide doctors with adequate information concerning the risks posed to under-represented populations.

Even when FDA receives proper data, however, it often lacks the skills to interpret it. In fact, FDA's own Science Board found that FDA lacks sufficient expertise in quantitative methods, such as statistics and biomathematics, to assess the products it regulates effectively or to guide sponsors to design valid and informative studies.[7]

As a result of the deficiencies, the U.S. Government Accountability Office ["GAO"] concluded that 51.5 percent of all approved drugs were associated with serious, post-approval risks, evidenced by labeling changes and withdrawals, that were not recognized before approval.[8]

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[7]FDA, *Science and Mission at Risk, Report of the Subcommittee on Science and Technology* 31, 35 [prepared for FDA Science Board] (Nov. 2007), *available at* http://www.chpa-info.org/ViewResource.ashx?id=4840.

[8]GAO, *Drug Safety: Post-Approval Risks 1975-1986* (Apr. 1990), at 3, http://archive.gao.gov/d24t8/141456.pdf.

FDA thus concedes that uncovering a prescription drug's safety profile also requires *post-marketing* monitoring.

> Although premarket testing discloses a general safety profile of a new drug's comparatively common adverse effects, the much larger patient population and longer period of use associated with the marketing of a drug provides, for the first time, the opportunity to collect information on rare, latent, and long-term effects, some of which may be serious.

FDA, *New Drug and Antibiotic Regulations, Final Rule*, 50 FED. REG. 7452, 7471 (Feb. 22, 1985). To that end, FDA regulations require that all drug manufacturers "establish and maintain records and make reports" to FDA about "[a]ny adverse event associated with the use of a drug in humans, whether or not considered drug related," after a drug has received federal approval, 21 C.F.R. §§314.80(a), (c), (j), and make ongoing ADR reports associated with their drugs. *Id.* §§314.80(c)(2)(i)-(ii), (j); 21 U.S.C. §355(e).

FDA has declared that "the primary objective of the adverse drug experience reporting system is to signal potential serious safety problems with marketed drugs ..." 50 FED. REG. at 7471. Based on receipt of "clinical or other experience, tests, or other scientific data," FDA may decide that an approved drug is no longer safe. 21 U.S.C. §355(e). It may ask that the drug be withdrawn or require revisions to its label "as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved." 21 C.F.R. §201.80(e); 21 U.S.C. §355(e). These regulations apply to generic drug manufacturers at all stages of a drug's marketing. *See, e.g.*, 21 C.F.R. §§201.57(c)(6); 201.80(e); 314.98(a).

B. Prescription Drugs May Be Sold in Generic Form Because Brand-Name Drugs Have Lost Their Legal Protections, Not Because Their Safety Profiles Have Been Definitively Established

When FDA approves the generic equivalent of a brand-name prescription drug, it does not render final judgment that either drug is safe. In fact, the Hatch-Waxman Act prohibits FDA from requiring that generic drug manufacturers conduct any new clinical studies before generic are approved. These manufacturers, however, must file an ANDA and show that their drugs are "bioequivalent" to an FDA-approved drug. 21 U.S.C. §355(j).

Once the ANDA has been approved, the Act affords manufacturers five years of labeling exclusivity for new uses or conditions or patent protection for discoveries capable of being patented but allows competition from generics once these protections end – and often long before. 21 C.F.R. §314.108(b)(2). The Act creates an exception to patent law [and claims of patent infringement] that allows generic drug manufacturers to use brand-name drugs still under patent to obtain bioequivalency data so that they will be ready to market generic equivalents the moment the brand-name manufacturers' protections end. 35 U.S.C. §271(e)(1).

Generic manufacturers may even seek approval to market generic versions of approved drugs *prior* to the expiration of the pioneer's patent or period of exclusivity by challenging the patent or certifying that it does not cover their product. 21 U.S.C. §355(j)(2)(A)(vii)(IV). Such applications may be filed

as early as 4 years after approval of an NDA. In fact, most patent challenges today are filed at the four-year mark because the first to file gains six months of exclusivity when generics are permitted to enter the market.[9] Given this short time frame, many drug risks may not emerge until after generics have captured the market, as the drugs discussed below demonstrate.

C. In Addition to Metoclopramide [Reglan], the Safety Profiles of Other Widely-Used Drugs Have Changed Dramatically Long After Generic Equivalents Were Approved

As with Reglan, the dangerous side effects of other prescription drugs are often identified years after they "go generic." The following drug histories demonstrate that it is both improper and dangerous to public health to assume, as Petitioners and their amici would have this Court do, that the safety profile of all generic drugs has necessarily been established upon approval of its ANDA.

1. Promethazine [Phenergan]

The history of promethazine illustrates the inability of FDA's post-marketing monitoring to detect catastrophic side effects, particularly those relating only to the means of administering a drug, even when

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[9] U.S. House of Representatives, Committee on Energy and Commerce, Subcommittee of Commerce, Trade and Consumer Protections, *How Pay-for-Delay Settlements Make Consumers and the Federal Government Pay More for Much Needed Drugs* (Statement of Diane E. Bieri) (Mar. 31, 2009), at 8.

hundreds of reports of those side effects have accumulated for decades in FDA's own database.

Phenergan, the drug that caused Diana Levine's injuries, *see Levine*, 129 S. Ct. at 1191, was the brand name for promethazine hydrochloride.[10] FDA approved its use in injectable form in 1956. *Id.* In June 2000, FDA permitted marketing of generic injectable promethazine. *Id.*, promethazine hydrochloride [ANDA 040372]. Wyeth no longer markets Phenergan. It is available today in only generic form.

Promethazine is an antihistamine.[11] Because it blocks certain neurotransmitters from activating areas of the brain that control nausea and vomiting, it was approved to treat allergic reactions, nausea, and motion sickness.[12] Promethazine, however, contains several irritating substances and also has a low pH compared to human bodily fluids; therefore, it essentially acts as an acid when the two come into

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[10] *See* FDA, Drugs@FDA, Phenergan [NDA 008857], *available at* http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails.

[11] Benjamin N. Galpern, *et al.*, *Experimental Research on a New Series of Chemical Substitutes with Powerful Antihistamine Activities: The Phenothiazine Derivatives*, 140 COMP. REND. SOC. BIOL. 361 (1946) (*Fr.*); Chiaki Kamei, *et al.*, *Participation of Histamine in the Step-Through Active Avoidance Response and its Inhibition by H1 Blockers*, 57 JAPANESE J. PHARMACOLOGY 473, 475 (1991).

[12] *See* Julie Golembiewski, *et al.*, *Pharmacological Prophylaxis and Management of Adult Postoperative/Postdischarge Nausea and Vomiting*, 21 J. PERIANESTHESIA NURSING 385, 388 (2006).

contact.[13] In situations like the one involving Diana Levine, promethazine damages an artery, cutting off blood flow to the surrounding areas, resulting in necrosis, gangrene, and amputation. *See Levine*, 129 S. Ct. at 1191. Even if it does not damage an artery, it may still cause nerve damage, phlebitis and thrombophlebitis, abscesses, and tissue necrosis, which may require skin grafts.[14]

Prior to 2006, few clinicians were aware of the dangers posed by "IV push" method of administration of promethazine. Until 2006, there were few published reports of inadvertent intra-arterial injection or extravasation[15] associated with promethazine. In fact, "[a] search of the primary literature ... produced no reports of extravasation of promethazine."[16] Another commentator writes that "[e]mergency department nurses are asked frequently to give this medication intravenous push, yet many are unaware of the risks associated with this practice and the serious outcomes

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[13] *See* Susan Paparella, *The Dangers of Intravenous Promethazine Administration*, 33 J. EMERGENCY NURSING 53, 54 (2007).

[14] *See* Baxter Pharms., *Phenergan Injection* (2005), http://www.baxter.com/products/anesthesia/anesthetic_pharmaceuticals/downloads/phenergan.pdf.

[15] "Extravasation" is the inadvertent administration of medication outside the vein and into the surrounding tissue. Carmel Sauerland, *et al.*, *Vesicant Extravasation Part I: Mechanisms, Pathogenesis, and Nursing Care to Reduce Risk*, 33 ONCOLOGY NURSING FORUM 1134, 1134 (2006).

[16] *See* Mark A. Malesker, *et al.*, *Extravasation of I.V. Prothazone*, 56 AM. J. HEALTH-SYS. PHARMACY 1742 (1999).

that may occur with intravenous administration." Paparella, *supra* note 13, at 55.

In August 2006, the Institute for Safe Medication Practices ["ISMP"], a well-respected scientific organization, published the first comprehensive report on the dangers of intravenous use of promethazine. ISMP recommended that promethazine be contraindicated for intravenous use, or that special precautions be used to avoid extravasation.[17]

Despite the absence of prior published reports, ISMP also concluded that there had been individual, unpublished reports of serious injuries associated with the intravenous use of promethazine for decades. "Promethazine extravasations that result in serious tissue damage are not rare; indeed, one in five respondents reported awareness of such an occurrence in their facility with the past five years."[18] Government data supports ISMP's conclusion.

ADR reports submitted to FDA are available to FDA, manufacturers, and the public in the Adverse Events Reporting System ["AERS"] database. *See* http://www.fda.gov/ceder/aers/default.hym. It reveals that, from 1969 [when records were first kept] until December 2006, 45.6% of the serious adverse event reports for intravenous promethazine involved reactions related to those listed in the ISMP report. This is compared to 15.7% of serious adverse events for other intravenous drugs involving similar reactions, a

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[17] *See* ISMP, *Action Needed to Prevent Serious Tissue Injury with IV Promethazine* (Aug. 10, 2006), http://www.ismp.org/newsletters/acutecare/articles/20060810.asp.

[18] *See* ISMP, *Promethazine Conundrum: IV Can Hurt More Than IM Injection!* (Nov. 2, 2006), http://www.ismp.org/newsletters/acutecase/articles/20061102.asp.

strong signal. There is no indication that FDA ever analyzed this data, kept on its own database, which revealed serious problems associated with intravenous administration of promethazine.

In September 2009, *53 years* after FDA first approved injectable promethazine, *9 years* after FDA permitted the marketing of its generic equivalent, *3 years* after the ISMP study was published, and *6 months after this Court memorialized Phenergan's catastrophic side effects in Levine*, 129 S. Ct. at 1191, FDA finally acted and required a "black box" warning, its strongest, for injectable promethazine concerning the risks the ISMP report revealed.[19]

2. SSRI Antidepressants

The history of SSRI antidepressants shows how tort lawsuits acted as a catalyst for the development of antidepressants' safety profile, uncovering critical data withheld by SSRI manufacturers, and moving an unduly-recalcitrant FDA to require appropriate, scientifically-substantiated, and life-saving warnings.

Prozac is the brand name for fluoxetine hydrochloride and the first of a class of SSRI antidepressants. *See* Drugs@FDA, *supra*, Prozac [NDA 018936]. In 1987, Prozac was approved for treatment of depression, anxiety, and other mood disorders in adult patients. *Id.* Generic forms of Prozac were first

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[19] *See* 21 C.F.R. §201.80(e); FDA, *Information for Healthcare Professionals - Intravenous Promethazine and Severe Tissue Injury, Including Gangrene* (Sept. 16, 2009), http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm182169.htm.

approved in 2001. *Id.*, fluoxetine hydrochloride [ANDA 074803].

Approved in 1992 for the same indication, Paxil is the brand name for paroxetine hydrochloride, another member of the SSRI antidepressant class. *See id.*, Paxil [NDA 020031]. Generic paroxetine hydrochloride was first approved for these indications in July 2003. *Id.*, paroxetine hydrochloride [ANDA 075356].

Scientists first recognized that suicidal thoughts and behaviors might occur because of the use of SSRIs themselves, rather than because of the underlying disease of depression, when two prominent Harvard psychiatrists published a study of fluoxetine in 1990.[20] They observed, "'[we have recently observed several complex patients who appear to have had serious paradoxical responses to fluoxetine [Prozac] that were characterized by intense, violent suicidal thoughts... the strong obsessive suicidal thoughts apparently emerged *de novo* after weeks or months of treatment." *Id.* at 209. In the years that followed, evidence of a link between SSRIs and suicide risks only grew stronger.

Nevertheless, the only mention of suicide in Prozac's initial labeling appeared in a precaution: "[t]he possibility of a suicide attempt is inherent in major depressive disorder and may persist until significant remission occurs."[21] Other antidepressant manufacturers later copied this language for their own labels. For the next seventeen years, there was no

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[20] *See* Martin Teicher, *et al.*, *Emergence of Intense Suicidal Preoccupation During Fluoxetine Treatment*, 147 AM. J. PSYCHIATRY 207 (Feb. 1990).

[21] *See Rimbert v. Eli Lilly & Co.*, 577 F. Supp.2d 1174, 1180-81 (D. N.M. 2008).

indication in any antidepressant label that SSRIs could be a part of the problem, rather than a part of the cure.

When two citizen petitions seeking withdrawal of Prozac or inclusion of suicide warnings arrived at FDA in 1990 and 1991, respectively, it responded by convening its Psychopharmacologic Drugs Advisory Committee. Despite the *Teicher* study, the Committee concluded that it had insufficient data to require any warning that Prozac could cause suicidal thoughts or actions.[22] This was true, in part, because of the poor quality of the data the Committee received. *Id.* at 185 ("We agree the data are not great quality data"). Although FDA asked Lilly "to develop plans to conduct new studies, including clinical trials and epidemiological studies, studies that could provide more direct answers to the questions that have been raised," no such studies were ever conducted or submitted to FDA. *Id.* at 128. FDA took no action against Lilly for its defiance.

Instead, even FDA looked to the courts to assist it in gaining answers and information. In response to the citizen petitions, it wrote that "an actual court finding of a causal relationship" would be significant in its decision-making. "In that event, the agency would be able to evaluate the scientific basis for the court's conclusion, and consider whether the court's conclusion warranted a modification of its own position."[23]

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[22]FDA, Psychopharmacological Drugs Advisory Committee, *Hearing Transcript*, at 126 (Rockville, Maryland) (Sept. 20, 1991), *available at* http://www.fda.gov/ohrms/dockets/ac/prozac/2443T1.PDF.

[23]Letter from Carl C. Peck, M.D. to Sanford Block, Executive Director of Citizens Commission on Human Rights (July 26, 1991), *available at* https://ecf.wyd.uscourts.gov/doc1/20715400

Such a ruling would be a long time coming. For almost a decade, lawyers fought to wrest information from SSRI manufacturers about suicide risks while some manufacturers took extraordinary – and even fraudulent – measures to hide it. *See Winkler v. Eli Lilly & Co.*, 101 F.3d 1196, 1199 (7th Cir. 1996).

After nine years of struggle in the courts, a unanimous federal jury in Wyoming found that Paxil "can cause some individuals to commit homicide and/or suicide." *Tobin v. SmithKline Beecham Pharms.*, 164 F. Supp.2d 1278, 1287-88 (D. Wy. 2001). This verdict was based on the trial court's finding that the plaintiff's suicide evidence was "scientifically reliable" and admissible under *Daubert v. Merrell Dow Pharms.*, 509 U.S. 579 (1993). *Tobin*, 164 F. Supp.2d at 1283.

By 2003, even Wyeth, the manufacturer of Effexor, another SSRI, sent out a "Dear Doctor" letter in which it warned of hostility and suicidality for pediatric patients taking Effexor XR, another SSRI antidepressant.[24] Other manufacturers later did the same with regard to adult patients.[25]

Finally, in 2004, FDA finally acknowledged what many in the scientific community had known for years. In March, it issued a Public Health Advisory, in which it asked all antidepressant manufacturers to warn

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01; *see Motus v. Pfizer*, 127 F. Supp. 2d 1085, 1100 n.13 (C.D. Cal. 2000), *aff'd*, 358 F.3d 659 (9th Cir. 2004).

[24] "Dear Healthcare Professional" Letter from Wyeth (Aug. 22, 2003), *available at* http://www.antidepressantsfacts.com/2003-08-22-Wyeth-Effexor-kids.pdf.

[25] "Dear Healthcare Professional" Letter from GSK (May 6, 2006), *available at* http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM153413.pdf.

about increased suicide risks for both children and adults.[26] Later that year, FDA requested that manufacturers of antidepressants add a "black box" warning to their respective labels, titled "Suicidality in Children and Adolescents."[27] FDA's Director of the Office of Drug Evaluation explained: "I think that we now all believe that there is an increase in suicidal thinking and action that is consistent across all the [SSRI] drugs..."[28]

In 2007, twenty years after FDA first approved Prozac, 16 years after studies revealed SSRIs' suicide risks, and six years after FDA approved the first generic SSRI, FDA finally requested that labels for all antidepressants include a class-wide section in which the "black box" would be changed from "Suicide in Children and Adolescents" to "Suicidality and Antidepressant Drugs."[29]

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[26] FDA, *Public Health Advisory* (Mar. 22, 2004), *available at* http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm161696.htm.

[27] FDA, *Labeling Change Request Letter for Antidepressant Medication* (Oct. 15, 2004), *available at* http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm096352.htm.

[28] Gardiner Harris, *F.D.A. Links Drugs to Being Suicidal*, THE N.Y. TIMES (Sept. 14, 2004), *available at* http://www.nytimes.com/2004/09/14/health/14depress.html?_r=1&oref=slogin.

[29] The current version of the class-wide section of the label appears at http://www.fda.gov/cder/drug/antidepressants/antidepressants_label_change_2007.pdf.

3. Gabapentin [Neurontin]

Gabapentin's history reveals how its suicide risks were hidden for years from the public, the medical community, and FDA by Neurontin's manufacturer's public denials and illegal promotion of its wide-ranging off-label use in the general population.

Neurontin is the brand-name for gabapentin. It was approved only for "adjunctive" therapy [use with another drug] for epilepsy in adults in 1993. *See* Drugs@FDA, *supra*, Neurontin [NDA 020235]. Although Parke-Davis, a division of Warner-Lambert, had filed patent applications for Neurontin for treatment of depression, neurogenerative disease, mania, and bipolar disease, it never sought FDA approval for any of these indications. *In re Neurontin Mktg. & Sales Practices & Prods. Liab. Litig.*, 612 F. Supp.2d 116, 122 (D. Mass. 2009). FDA later denied Warner-Lambert/Pfizer's application for approval of Neurontin as monotherapy for partial seizures, as well as their efforts to increase its maximum dosage.[30] Without FDA approval, federal law prohibited these manufacturers from marketing or promoting Neurontin for these "off-label" uses. Against this backdrop, FDA approved the use of generic gabapentin in 2003. Drugs@FDA, *supra*, gabapentin [ANDA # 075350].

Evidence of an association between the use of gabapentin and depression and suicidal thoughts and

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[30] *See In re Neurontin Mktg. & Sales Practices & Prods. Liab. Litig.*, 618 F. Supp.2d 96, 103 (D. Mass. 2009). In May 2002, FDA did approve Neurontin for management of post-herpetic neuralgia (pain resulting from nerve damage caused by shingles or herpes zoster) in adults. Drugs@FDA, *supra*, Neurontin [NDA 021397].

behaviors emerged as early as Neurontin's pre-approval clinical trials in 1992. Because Neurontin was to be used only in a very limited population [adult epileptics], however, FDA found Neurontin "approvable with appropriate and prominent labeling *for use in a specific population*."[31] Thus, in 1994, Neurontin's label included only mention of depression and "suicide gesture" as adverse events observed during clinical trials.[32]

Beginning in 1995, however, Warner-Lambert, later Pfizer, Neurontin's manufacturer, began illegally to promote the sale of Neurontin for "off-label" uses, such as the treatment of pain, bipolar disorder and anxiety. *In re Neurontin*, 618 F. Supp.2d at 102. Warner-Lambert ultimately pleaded guilty to improper promotion of off-label use, among other offenses, and paid a $430 million fine in June 2004, the year after FDA permitted marketing of generic gabapentin.[33]

During this illicit national marketing campaign, Warner-Lambert/Pfizer not only failed to disclose or warn that Neurontin may be associated with depression and suicidality, their representatives favorably compared Neurontin with competing drugs which had specific suicide warnings. *Id.* at 103. Worse, Pfizer's

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[31] *See In re Neurontin*, 618 F. Supp.2d at 102 (quoting FDA approval of Neurontin NDA) (emphasis supplied).

[32] Drugs@FDA, *supra*, Neurontin, [NDA 020235]; *In re Neurontin Mktg. & Sales Practices & Prods. Liab. Litig.* 2010 U.S. Dist. LEXIS 116876, *11-12 (D. Mass. Nov. 3, 2010).

[33] *See In re Neurontin*, 618 F. Supp.2d at 104; U.S. Department of Justice, *Press Release: Warner-Lambert to Pay $430 Million to Resolve Criminal & Civil Health Care Liability Relating to Off-Label Promotion* (May 13, 2004), *available at* http://www.justice.gov/opa/pr/2004/May/04_civ_322.htm.

Senior Medical Director denied *any* association between Neurontin and suicidality on National Public Radio in 2003: "'[T]here is ***absolutely no evidence*** that Neurontin ... has been associated with suicidal behavior or that it can cause suicidal behavior.'" *Id.* (emphasis supplied). As a result of Warner-Lambert/Pfizer's promotion of Neurontin and denial of its dangerous side effects, sales of Neurontin for a host of indications and populations sky-rocketed. *Id.* Approval to market generic equivalents was granted that year.

By January 2008, the side effects of Neurontin and its generic counterparts could no longer be concealed. Fifteen years after Neurontin was approved for limited use in specific populations, and five years after generic substitutes were approved for limited indications, FDA finally issued an "alert" warning physicians to "[b]e aware of the possibility of the emergence or worsening of depression, suicidality, or any unusual changes in behavior" in patients taking gabapentin. *In re Neurontin*, 2010 U.S. Dist. LEXIS 116876, at *23.

4. Isotretinoin [Accutane]

The history of isotretinoin illustrates how critical safety information about prescription drugs can be masked for years behind inadequate warnings and manufacturers' efforts to withhold information.

Accutane is the brand-name for isotretinoin, developed by Roche and approved by FDA in 1982 to treat recalcitrant nodular acne. Drugs@FDA, *supra*, Accutane [NDA 018662]. Several generic equivalents of Accutane have been approved by FDA, starting in April 2002. *Id.* Roche withdrew Accutane from the

market in 2009.[34] Only generic substitutes are available today.

Prior to receiving FDA approval to market Accutane, Roche conducted several studies that revealed potential stomach and/or intestinal side effects. In one clinical study of 523 patients, 21.6 percent reported some gastrointestinal problems associated with using Accutane.[35] Pre-approval animal studies also revealed gastrointestinal bleeding in dogs that were administered the drug. *Id.* Nevertheless, FDA approved Accutane without requiring that Roche include warnings about inflammatory bowel disease ["IBD"] in its original label. *Id.* at *13.

IBD describes a chronic inflammation of the small bowel and the colon. *Id.* at *3. It typically presents as one of two diseases: Crohn's disease or ulcerative colitis. *Id.* Ulcerative colitis is a chronic inflammation and ulceration of the inner lining of the cells of the colon and rectum. *Id.* Crohn's disease is similar to ulcerative colitis but can attack any part of the digestive tract. *Id.* IBD is a permanent condition, although the symptoms may remit and recur. *Id.* It often requires removal of the colon. *Id.*

In 1983, FDA received a citizen petition seeking enhanced warnings on Accutane about a variety of adverse reactions, including IBD. *Id.* at *14. The petition asserted that "clusters of serious reactions [from ADR reports] are unlikely to be related to factors

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[34] *See Roche Discontinues and Plans to Delist Accutane in the U.S.* (June 29, 2009), http://www.rocheusa.com/portal/usa/search?communityId=re7180004&search_input=accutane&file_type=&_requestid=321420.

[35] *See Kendall v. Hoffman-La Roche, Inc.*, 2010 N.J. Super. LEXIS 1904, *4 (App. Div. Aug. 5, 2010) (unpublished).

other than the drug." *Id.* Despite these reports, FDA did not require any change in Accutane's labeling.

In March 1984, however, Roche itself made very modest revisions to its warnings and physician information about Accutane. In both, it stated only that Accutane had been "temporally associated" with IBD. *See Kendall*, 010 N.J. Super. LEXIS 1904 at *15; Drugs@FDA, *supra*, Accutane [Labels]. Having donned this regulatory burqa, Roche apparently felt free to ignore the link between isotretinoin and IBD. It never conducted any studies or clinical trials on IBD during the remaining years it sold Accutane.

Roche's early internal reports, however, revealed "38 case reports of colitis and proctitis in association with [isotretinoin] treatment." *McCarrell v. Hoffman La Roche, Inc.*, 2009 N.J. Super. LEXIS 558, *16 (App. Div. Mar. 12, 2009) (unpublished). Roshe's physician reviewer thus recommended that "Roche ... further monitor closely cases of colitis and proctitis reported in association with [isotretinoin] treatment." *Id.* at *16-17. A later reviewer announced, after uncovering 104 cases of colitis and related symptoms, that "it is reasonable to conclude from these data, that in rare cases, [isotretinoin] may induce or aggravate a preexisting colitis." *Id.* at 15.

It is unclear if the ADR reports Roche reviewed made it to FDA in a timely fashion. In 1998, FDA issued a warning letter to Roche for failing to submit serious adverse event reports to FDA regarding Accutane in a timely manner when it was revealed that FDA had not received from Roche some ADR reports regarding Accutane, dated in *1991*, until *1997*.[36]

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[36] James O'Donnell, *et al.*, DRUG INJURY: LIABILITY, ANALYSIS, AND PREVENTION 348 (2005).

In 2000, 18 years after its approval, FDA approved a label change for Accutane, removing the word "temporally" from the description of IBD and warning that the symptoms of IBD "have been reported to persist after Accutane treatment has stopped ..."[37]

In 2006, four years after FDA approved generic isotretinoin, Massachusetts General and University of Chicago Hospitals issued a comprehensive study of isotretinoin and IBD.[38] The authors obtained every pertinent MedWatch report filed with FDA and reviewed all ADR reports filed with Roche involving isotretinoin and IBD. *Id.* at 1569-70. The study concluded that "in the cases reported to the FDA between 1997 and 2002, isotretinoin appears to be a potential precipitant of IBD." *Id.* at 1572. The authors recommended warning doctors and patients about these side effects.

It was not until 2010, however, 18 years after Accutane's approval, 8 years after generics were first approved, and one year after Accutane was removed from the market, that an independent epidemiological study was published that showed a statistically-significant increase in the risk of ulcerative colitis, a form of IBD, with isotretinoin-use.[39]

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[37]FDA, Drugs@FDA, Accutane [Labeling Revision] (May 5, 2000), *available at* http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory.

[38]*See* Deepa Reddy, M.D., *et al.*, *Possible Association Between Isotretinoin and Inflammatory Bowel Disease*, 101 AM. J. GASTROENTEROLOGY 1569 (2006).

[39]Seth D. Crockett, *et al.*, *Isotretinoin Use and the Risk of Inflammatory Bowel Disease: A Case-Control Study*, 105 AM. J. GASTROENTEROLOGY 1986, 1990, 1991 (2010) (finding also that higher doses of isotretinoin augment UC risk).

If this Court shields generic isotretinoin manufacturers from tort liability, they will have no incentive to update their labeling to reflect this new and important information and there is no longer a brand-name manufacturer to communicate this information for them.[40] Petitioners do not tell this Court who will warn patients and doctors if the remaining generic manufacturers do not.

What should be clear from these histories is that it often takes decades before a drug's safety profile fully emerges, sometimes long after generics have supplanted their brand-name counterparts. Second, they show that FDA action has historically reflected and recognized a drug's evolving safety profile, not defined it. Equally important, they illustrate FDA's limited ability actually to protect the public against pharmaceutical risks, particularly in the face of drug manufacturers' efforts to conceal those risks, and the crucial role the tort system has played in uncovering critical drug safety information.

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[40] Once name-brand manufacturers remove their products from the market in favor of generics, there is often no listing at all for either the brand-name drug or its generic equivalents in the PDR, the "Bible" on prescription drugs for most physicians. Without such listings or other communications, the typical dermatologist, who would most likely prescribe isotretinoin, is unlikely to see the AMERICAN JOURNAL OF GASTROENTEROLOGY, a specialty journal.

II. FDA ALONE CANNOT ENSURE GENERIC DRUG SAFETY BECAUSE IT *STILL* LACKS ADEQUATE INFORMATION, RESOURCES, AND AUTHORITY TO MONITOR AND PROTECT THE PUBLIC AGAINST PHARMACEUTICAL RISKS

Petitioners and their industry amici resurrect the argument, rejected in *Levine*, 129 S. Ct. at 1199, that drug labels approved by FDA constitute both a "ceiling" and "floor" on what information manufacturers are required to present to doctors and patients about approved drugs. Unless FDA is freed from the meddling of judges and juries, they contend that it will be unable to strike the proper balance between drug safety and efficacy and public health will suffer.

As demonstrated above, however, FDA has historically *relied* on the tort system to uncover critical drug safety information. In fact, this Court has recognized that "state tort suits uncover unknown drug hazards and provide incentives for drug manufacturers to disclose safety risks promptly. They also serve a distinct compensatory function that may motivate injured persons to come forward with information." *Id.* at 1202.

Equally important, in making their argument, Petitioners and their *amici* rely on three assumptions, none of which has any basis in FDA's actual operations. First, they assume that FDA has the necessary time, resources, and tools to fulfill its responsibilities; second, that FDA receives or can acquire sufficient information to strike the proper balance between safety and efficacy; and third, that it has sufficient authority both to acquire missing information and to enforce its requests. All three assumptions are incorrect.

A. FDA's Responsibilities Far Outstrip the Resources It Has to Address Them

FDA regulates products constituting 25% of the U.S. gross domestic product,[41] including more than 11,000 drugs through CDER.[42] FDA approves several hundred new and generic drugs each year and analyzes hundreds more. FY 2009 Report at 103. Yet, as this Court has recognized, "[F]DA has limited resources to monitor the 11,000 drugs on the market..." *Levine*, 129 S. Ct. at 1202. Since *Levine*, the problem has only grown worse.

CDER has recently experienced a dramatic increase in workload, particularly with regard to generic drugs. The number of ANDAs has almost doubled over the past 6 years, a period when staffing levels increased by only 20%. FY 2009 Report at 6, 82, 92. In FY 2009, CDER approved, or tentatively approved, 599 applications to market generic versions of prescription drugs, the equivalent of *more than two approvals and tentative approvals each business day of the year*. *Id.* at 103. In sum, CDER took 2,006 actions in FY 2009, including approvals, tentative approvals, not approvable, and approvable actions on applications, compared to 1,934 in FY 2008. *Id.* at 103.

Once a drug is approved, FDA's responsibilities for monitoring drug safety mount. The number of adverse

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[41] Bruce M. Psaty & R. Alta Charo, *FDA Responds to Institute of Medicine Drug Safety Recommendations – In Part*, 297 JAMA 1917, 1917-19 (2007).

[42] FDA, CDER, *2005 Report to the Nation: Improving Public Health Through Human Drugs* 12 ["FDA 2005 Report"], http://www.fda.gov/downloads/AboutFDA/.../CDER/.../UCM078935.pdf.

event reports submitted to CDER annually reached over 522,871 in FY 2008 and was projected to be over 600,000 by FY 2010. *Id.* at 83. Increasingly, FDA receives citizen petitions for FDA actions on ANDAs. *See* 21 C.F.R. §10.30. Citizen petitions may be used by stakeholders outside of FDA to ask it to take – or refrain from taking – action. FDA has received numerous petitions asking it not to approve particular generic drugs unless certain criteria set forth in the petitions are met. In most cases, these petitions raise scientific issues relating to the standards for approval of ANDAs. CDER must evaluate and respond to each of these petitions. *See* FY 2009 Report at 83.

In addition, there are more than 6,000 FDA-regulated drug manufacturing facilities worldwide for FDA to inspect. *Id.* at 105. This crushing burden has led FDA to engage in regulatory triage. It explained: "FDA's current performance metric for quality is focused on optimizing the allocation of a limited drug inspection force and increasing the number of inspections among those facilities rated as high risk." *Id.* Thus, in FY 2008, FDA's Office of Regulatory Affairs conducted just 132 foreign site pre-approval inspections. *Id.* at 83.

Finally, FDA is also responsible for food safety and protecting the public from a rising tide of food and drug imports. In 2007, the United States imported more than $2 billion worth of FDA-regulated products, from roughly 200 countries or territories, using 825,000 importers, through over 300 U.S. ports-of-entry.[43]

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[43]FDA, Office of International Programs, Murray Lumpkin, Deputy Commissioner, *Embassy Briefing* (Dec. 1, 2009), *available at* http://www.fda.gov/InternationalPrograms/InternationalCommunications/EmbassyBriefings/ucm202894.htm.

It is little wonder that three recent analyses of FDA's drug safety oversight – two by GAO and one by IOM – criticized FDA's inability to keep unsafe drugs off the market and to respond effectively to observed hazards.[44] In particular, IOM observed:

> FDA does not have adequate resources or procedures for translating preapproval safety signals into effective post-marketing studies, for monitoring and ascertaining the safety of new marketed drugs, for responding promptly to the safety problems that are discovered after marketing approval, and for quickly and effectively communicating appropriate risk information to the public.

IOM Report at S1-2-1-3c. It *still* does not.

B. FDA's Post-Marketing Monitoring Is Insufficient to Protect the Public Against Pharmaceutical Risks

Contrary to what many in the public believe, FDA itself does not perform any independent studies or clinical trials on either the new or generic drugs it approves. Instead, it relies on information received from manufacturers during the INDA, NDA, and ANDA processes and on "[a] passive and largely voluntary system of adverse event reporting to monitor the safety

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[44] *See* GAO, *Drug Safety: Improvement Needed in FDA's Post-market Decision-Making and Oversight Process* (2006), http://www/gao.gov/cgi-bin/getrpt?GAO-06-402 ["GAO 2006 Report"]; GAO, *Drug Safety: FDA's Oversight of the Promotion of Drugs for Off-label Uses*, http://www.gao.gov/news.items/d088835.pdf; Institute of Medicine of the Nat'l Academy of Science, *The Future of Drug Safety* (Baciu, Alina, *et al.*, eds., 2006) [IOM Report"].

of drug products on the market." FY 2009 Report at 107. Both sources are fatally flawed.

As demonstrated above, inherent and practical limitations on the information FDA receives from clinical trials mean that the safety profile of a drug cannot be fully known when FDA approves it.

Even when a drug is approved, however, FDA is still at the mercy of others to supply it with information on the safety of approved drugs. Janet Woodcock, CDER's Director, the office responsible for monitoring prescription drug safety, described FDA's historic approach to post-approval monitoring as follows: "you [the manufacturer] do the clinical trial, throw the drug over the wall [from FDA's perspective], and then send us your Medwatch reports and let us know what happens."[45]

FDA attempts to monitor drugs' post-approval performance by gathering reports of ADRs through its AERS and "MedWatch" programs. 21 C.F.R. §310.305 (2008). The Government recognizes, however, that only about 1% of actual adverse drug reactions is ever reported to FDA or manufacturers.[46] Even when reports are received, however, they may be of limited utility

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[45]Catherine Varmazis, *CDER Stresses "Active" Post-Approval Surveillance*, BIO.ITWORLD.COM (June 16, 2008) (quoting Janet Woodcock), *available at* http://www.postapproval.org/articles.htm.

[46]*See, e.g.*, Veterans Health Administration, Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel, *Review of the Efficacy and Safety of Propoxyphene* 8, n.15 (March 2006), http://www.pbm.va.gov/Clinical%20Guidance/Drug%20Class%20Reviews/Propoxyphene,%20Drug%20Review.pdf; FDA, CDER, *The Clinical Impact of Adverse Drug Event Reporting* 5 (1996), http://www.fda.gov/medwatch/articles/medcont/medcont.htm; IOM Report at 53.

since FDA ordinarily does not receive information about how many people use the drug so that it can calculate the incidence of the ADR.[47]

Worse, there is a growing consensus that some information is simply not accessible from spontaneous reporting systems, such as the long-term effects of medications, reliable comparisons between products, and rare adverse effects associated with older drugs, the ones most likely to have generic equivalents.[48] Phenergan is a tragic example of this deficiency. Moreover, although spontaneous reporting can assist in signal detection for rare cases of severe toxicity, it is less effective in detecting adverse events that commonly manifest in the general population, such as cardiovascular complications of COX-2 inhibitors such as Vioxx. *Id.* at 433, n.18.

These deficiencies are especially problematic because of FDA's historic inability to order and insure that manufacturers actually conducted and submitted post-approval studies. GAO 2006 Report at 28. FDA estimated that 1,231 post-approval studies were overdue as of September 2005, more than 75% of which had not even been initiated.[49] As demonstrated below,

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[47] *See* Charles Steenburg, *The Food and Drug Administration's Use of Post-Marketing (Phase IV) Study Requirement: Exception to the Rule?*, 61 FOOD & DRUG L.J. 295, 298, n.30 (2006).

[48] David B. Ridley, *et al.*, *Spending on Postapproval Drug Safety*, 25 HEALTH AFFAIRS 429, 433 n.17 (2006), *available at* http://content.healthaffairs.org/content/25/2/429.full.

[49] *See* FDA, *Report on the Performance of Drug and Biologics Firms in Conducting Post-Marketing Commitment Studies*, 71 FED. REG. 10978-79 (2006).

even FDA's new authority to order post-approval studies may not measurably improve this situation.

C. New FDA Authority is Inadequate to the Ensure Generic Drug Safety

Congress passed the FDAAA in 2007 to improve post-marketing monitoring and prescription drug safety. As CDER's Director explained: "It's a response by Congress to what they saw as FDA's weaknesses."[50] Yet even she admits that FDA's new authority is quite limited and unlikely to remedy the problems it was intended to solve. This, this Court should not assume that FDAAA's passage renders FDA capable of ensuring drug safety without the support of the tort system[51]

Although the FDAAA empowers FDA to order post-approval studies or clinical trials from drug manufacturers, it can do so only under very limited circumstances. 21 U.S.C. §355(o)(3)(A), (B). Dr. Woodcock explained: "'We have to make a finding that the study is really needed because we can't find the information out in other ways,'" *FDA's Woodcock on FDAAA*, *supra*, that is, FDA must find that its *own* "active postmarket risk identification and analysis system" will be "insufficient" for the purpose. 21 U.S.C. §355(o)(3)(D)(i). Moreover, manufacturers can appeal such orders. *Id.* §355(o)(3)(F).

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[50] *FDA's Woodcock on FDAAA*, CLINPAGE CLINICAL TRIAL NEWS (May 27, 2008), http://www.clinpage.com/article/fdas_woodcock_on_fdaaa/C9 (quoting Janet Woodcock).

[51] The facts giving rise to the cases before this Court occurred before the effective date of the FDAAA. As a result, it does not apply in them.

Similarly, the FDAAA authorizes FDA to notify drug manufacturers when it becomes aware of safety information it believes should be included in drug labeling and to order a change. *Id.* §355(o)(4)(A). The manufacturer can propose label changes or notify FDA that none is warranted. *Id.* §355(o)(4)(B). If FDA disagrees with the response, it must initiate "discussions" with the manufacturer. *Id.* §355(o)(4)(C). Thus, FDA must still "rel[y] on the prospect of productive negotiations with industry," a process that "leaves potentially critical regulatory action vulnerable to a subjective and highly variable process of exercising individual or agency influence, and to the vicissitudes of changing politics and attitudes toward regulation," the approach IOM criticized in 2006. IOM Report at S-9.

While negotiations may last only 30 days; FDA has the power to grant extensions. 21 U.S.C. §355(o)(4)(D). If the parties cannot agree, FDA may order the manufacturer to comply. *Id.* §355(o)(4)(G). Dr. Woodcock notes, however, "'but – here again – are the caveats. The sponsor can appeal this.'" *FDA's Woodcock on FDAAA*, *supra*; 21 U.S.C. §355(o)(4)(F). The FDAAA does not, therefore, give FDA the power to act unilaterally or immediately. At best, it can "accelerate" already-protracted timelines. *Id.* §355(o)(4)(H).

The FDAAA also purports to establish a massive, multi-source health database that will "compile pharmacoepidemiological data through electronic medical health records [EMRs] and medical claims databases" and cover *100 million Americans* by 2012.[52] Yet only 13 percent of doctors and 7.6 percent of

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[52]Kelly Davis, *et al.*, *New Directions in Monitoring Post-Approval Drug Safety*, GOOD CLINICAL PRACTICE JOURNAL 14, 15 (May 2009).

hospitals in the United States currently have *access* even to basic electronic record systems; the figures are lower (4 percent and 1.5 percent, respectively) for comprehensive, fully-functional systems.[83] Worse, health data is dispersed among multiple providers and insurers in both the public and private sectors. Medicare patients, on average, see six different doctors per year.[84] Thus, FDA must somehow marshal these fragmented data into a useful resource.[85] With just $11.2 *million* in its 2008 budget for modernizing drug safety, it is unlikely FDA can do so.

Moreover, FDA does not have legal authority to require diverse entities to make data available for post-marketing monitoring because of privacy and constitutional concerns.[86] Questions of due process and accountability could chill private-sector willingness to

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[83] Catherine DesRoches, *et al.*, *Electronic Health Records in Ambulatory Care – A National Survey of Physicians*, 359 NEW. ENG. J. MED. 50, 56 (2008); Ashish Jha, *et al.*, *Use of Electronic Health Records in U.S. Hospitals*, 360 NEW ENG. J. MED. 1628, 1632 (2009).

[84] U.S. House of Representatives, Subcommittee on Ways and Means, *Promoting Disease Management in Medicare* (Apr. 16, 2002) (statement of Dr. Gerard Anderson), at 5.

[85] *See* Carol C. Diamond, *et al.*, *Collecting and Sharing Data For Population Health: A New Paradigm*, 28 HEALTH AFFAIRS 454, 456, 460 (2009); Richard Platt, *et al.*, *The New Sentinel Network – Improving the Evidence of Medical-Product Safety*, 361 NEW ENGL. J. MED. 645, 647 (2009).

[86] *See* Mark A. Rothstein, *Health Privacy in the Electronic Age*, 28 J. LEGAL MED. 487, 489 (2007); Nicholas P. Terry & Leslie P. Francis, *Ensuring the Privacy and Confidentiality of Electronic Health Records*, 2007 U. ILL. L. REV. 681, 700 (2007) (discussing privacy concerns with large health databases).

participate. Without their participation, monitoring will be no better in the future than it is today.

Yet even if FDA can collect this data, "'figuring out how to analyze the data is going to be [FDA's] problem. It's going to be harder than anyone thinks,'" and particularly, "'difficult to do until we have better analytic tools.'" *FDA's Woodcock on FDAAA*, *supra*. As demonstrated above, it lacks those tools today.

For these reasons, the FDAAA did not provide FDA with the information, resources, or authority that would be essential to establish conclusively drug safety profiles or to protect the public from pharmaceutical risks without the critical assistance of the tort system.

CONCLUSION

The decisions of the courts below should be affirmed.

Respectfully submitted,

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AMICUS CURIAE BRIEF

Nos. 09-993, 09-1039, and 09-1501

Supreme Court, U.S.
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IN THE

Supreme Court of the United States

PLIVA, INC., ET AL.,

Petitioners,

v.

GLADYS MENSING,

Respondent.

ACTAVIS ELIZABETH, LLC,

Petitioner,

v.

GLADYS MENSING,

Respondent.

ACTAVIS INC.,

Petitioner,

v.

JULIE DEMAHY,

Respondent.

ON WRITS OF CERTIORARI TO THE UNITED STATES COURTS OF APPEALS FOR THE EIGHTH CIRCUIT AND FOR THE FIFTH CIRCUIT

BRIEF FOR MARC T. LAW, JOHN ABRAMSON, JULIE DONOHUE, MICHAEL FISCHER, AND MEREDITH ROSENTHAL AS *AMICI CURIAE* IN SUPPORT OF RESPONDENTS

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INTEREST OF *AMICI CURIAE*[1]

Amici are practitioners and professors who teach and write on various aspects of pharmaceutical regulation and the delivery of healthcare. *Amici* are filing this brief as individuals.

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1. The parties have lodged letters with the Court consenting generally to the filing of all briefs by *amicus curiae*. No counsel for any party in the above-captioned cases authored this brief in whole or in part and no person or entity other than *amici* or their counsel has made a monetary contribution to the preparation or submission of this brief.

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SUMMARY OF ARGUMENT

Amici support the view of the respondents and the circuit courts: Congress has not preempted state-law failure-to-warn claims brought against manufacturers of generic drugs.

Generic drugs constitute over three-quarters of the distributed prescription drugs in the United States, typically comprising well over 90% of prescriptions for a pill that has "gone generic." The Drug Price Competition and Patent Term Restoration Act of 1984 ("Hatch-Waxman"),[2] state generic substitution laws, lower reimbursement rates, and other institutional incentives have all combined to propel twenty-five years of generic pharmaceutical industry growth, which now amounts to $60 billion in U.S. sales annually. But the Hatch-Waxman incentives were intended to provide a means to deliver less expensive, *yet equally safe*, drug products. States should not be foreclosed from enforcing failure-to-warn laws that provide needed incentives to generic drug manufacturers to report to the FDA information that manufacturers learn about safety risks or signals concerning these widely used products.

State-law failure-to-warn litigation plays an essential role in promoting drug safety. Significant imbalances in the availability of safety-related information are inherent in the approval of pharmaceutical products, whether through a new drug application ("NDA") to the FDA or an abbreviated one ("ANDA"). While branded

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2. Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified at 21 U.S.C. § 355(b), (j), (l); 35 U.S.C. § 156, 271, 282).

manufacturers generally have greater access to their own unpublished drug-specific risk information than do generic manufacturers, the appropriate comparison is not between branded and generic manufacturers but between a product's manufacturer and consumers. Generic manufacturers are not ignorant of the safety risks of their products, and are often in a far better position than patients or physicians to know the accumulating risk information about their particular product. State-law failure-to-warn litigation mitigates this information asymmetry by aligning the incentives of drug manufacturers and consumers. State-law suits serve to: (1) supplement the FDA's inadequate resources to monitor comprehensively the performance of every drug on the market, (2) provide a strong incentive to drug manufacturers to respond to signals of health risks and seek action from the FDA, and (3) provide consumers with recourse in the event that drug manufacturers fail to strengthen or add warnings about their products when appropriate.

Creating significant post-approval incentives for drug manufacturers to report known safety information is especially important for generic manufacturers. Generic drug usage has increased steadily for decades, and it appears that significant institutional efforts will increase that percentage beyond the 75% of U.S. prescriptions currently filled by generic drugs. Within the first year of a drug "going generic," generic substitution laws and institutional formulary requirements typically shift as much as 90% of all prescriptions from the branded to the generic product. Many drugs are available *solely* in generic form: nearly one-third of all drugs have no brand volume at all. Risk information is increasingly sent to

the manufacturers – now generic manufacturers – of the product. In short, the vast majority of prescriptions written after brand exclusivity expires are filled with generic products; to the extent this places the generic manufacturer in a position of acquiring safety risk or signal information, that manufacturer should be incentivized to share such information.

Further, branded drugs are frequently approved after only short-term safety studies have been conducted; the long-term effects of a drug frequently are not reported for many years. The expiration of a drug's statutory exclusivity has nothing to do with when important, long-term safety risk information may become known; it is irrational to link the need for disclosure of such risks to the timing of expiration of exclusivity.

State-law failure-to-warn litigation does not, as the petitioners' *amici* contend, result in generic manufacturers submitting to the FDA risk information that the FDA "neither wants nor needs." The FDA is, after all, in the business of protecting the public's health. Although manufacturers have always faced state-law failure-to-warn liability, history shows that rather than *over*-report risk information for drug products (as a means by which to head off potential, long-term tort liability), manufacturers *under*-report risk information (as a means to maximize short-term profitability). The incentive to under-report is at least as strong for a generic manufacturer and state-law failure-to-warn claims provide counterbalancing incentives to make these important disclosures.

Petitioners' *amici* simply ignore the social and economic benefits of increased reporting of important safety information and the dual realities that (1) drug manufacturers have strong incentives to maximize profits, and (2) these profit-maximizing incentives may be misaligned with public health interests. They assume that the FDA can continuously optimize its regulatory standard throughout a drug's lifecycle and is equipped to address all health risk issues without the aid of reporting incentives on drug manufacturers. But the assumption is incorrect: information asymmetries, budget inadequacies, and regulatory realities limit the FDA's enforcement abilities. The FDA's tools for gathering post-approval information are relatively crude and ineffective. The lack of high-quality information and the limits on FDA enforcement power severely undermine the FDA's ability to effectively regulate what physicians and patients know about a drug once it is on the market. Accordingly, the tort system encourages manufacturers to act reasonably in warning the healthcare community about newly emerging risks and helps ensure that important risk information is provided to the FDA.

Petitioners' *amici* assert, without empirical data or real analysis, that a state-law duty to disclose known health risk or signal information would result in such huge economic costs as to nearly "wipe out" the reduction in drug costs created by the Hatch-Waxman scheme. This assertion is unsupported and dubious. Generic manufacturers are highly sophisticated, heavily-regulated organizations that have sweeping FDA reporting obligations. They persevere through lengthy ANDA application processes to demonstrate product bioequivalency and manufacturing

capabilities to mass-produce products that perform the same as branded products. There is no economic evidence that tort liabilities have (or would ever) cripple the branded pharmaceutical industry; there is similarly no evidence that the prospect of tort liability (tailored to the circumstances of a company marketing a drug product through ANDA approval) does anything other than require effective reporting of known risks.

Finally, there is no reason to think that Hatch-Waxman was designed, as the generic *amici* contend, to preempt any state-law measure that might impose economic costs on generic manufacturers. Numerous laws in innumerable ways impose costs on businesses; Hatch-Waxman was not intended to give generic manufacturers a free pass through the laws of the states with a single-minded purpose of keeping industry overhead costs reduced. Hatch-Waxman is part of the overall scheme to provide incentives for less expensive, *but equally safe*, medications available to the public.

ARGUMENT

I. THE GENERIC PHARMACEUTICAL INDUSTRY IS HIGHLY-REGULATED, SOPHISTICATED, AND PROFITABLE

A. Research, Development, and Approval of Generic Drugs Takes Time, Expertise, and Compliance with Multiple Federal Regulations

To obtain approval of a generic drug, a manufacturer must file an abbreviated new drug application ("ANDA"), a procedure defined by the Hatch-Waxman Act.[3] Hatch-Waxman simplified the approval of generic drugs by eliminating the need to prove independently that the generic is safe and effective; rather, generic manufacturers may rely on the scientific finding of safety and effectiveness demonstrated by the NDA so long as the manufacturer can demonstrate that the generic is bioequivalent to the branded product.[4] Where it does, the FDA may approve the ANDA as an AB-rated or bioequivalent generic version of the branded drug.

Branded manufacturers hold their production processes as trade secrets; demonstrating bioequivalence, therefore, is not merely a matter of replicating a recipe or composition.[5] Generic manufacturers must

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3. Fed. Food, Drug, & Cosmetic Act, 21 U.S.C. § 355(j); 21 C.F.R. § 314.94 (2011).

4. 21 U.S.C. § 355(j)(2)(A)(iv).

5. 21 C.F.R. § 314.430(g)(1) (manufacturing methods or processes not available for public disclosure by FDA). *See* Current Good Manufacturing Practice in Manufacture, Processing, Packing, or Holding, 43 Fed. Reg. 45,014, 45,024 (Sept. 29, 1978)

use independent expertise to formulate their drugs and conduct both laboratory and clinical testing to ensure that their products are absorbed equally to their branded counterparts. Generic manufacturers must also comply with the same elaborate chemistry, manufacturing, and controls ("CMC") requirements as branded manufacturers.[6] These general statutory quality standards are the same for NDA and ANDA applicants. Different companies satisfy the standards in different ways, often using proprietary methodologies known only to the particular manufacturer. As a result, generic companies develop their own proprietary manufacturing processes.

ANDA requirements ensure that AB-rated generic equivalents perform substantially the same as the branded drug (i.e., they are bioequivalent) – but the generic is rarely *exactly* the same as the branded product.[7]

(later codified at 21 C.F.R. pts. 210-11) ("many production and control processes are considered by individual firms to be trade secrets").

6. 21 C.F.R. § 314.50(d)(1) (CMC requirements); *id.* at § 314.94(a)(9) (making CMC requirements applicable to ANDAs); for the scope of CMC requirements, *see generally Chemistry, Manufacturing, and Controls (CMC)*, U.S. Food & Drug Admin., http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064979.htm (last visited Feb. 28, 2011); *Generics*, U.S. Food & Drug Admin., http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064995.htm (last visited Feb. 28, 2011).

7. A generic is only ever "exactly the same as" the branded when the manufacturer of the branded drug sells the exact same pills it previously sold as the branded drug as a generic equivalent. These identical generics make up a very small percentage of the market for generic drugs.

The composition of the generic may differ from the branded product: generics often use different forms of the active pharmaceutical ingredient (such as a calcium salt formulation instead of a sodium salt formulation) or different inactive ingredients. Generic manufacturers often purchase their active pharmaceutical ingredient from a different supplier. Generics may be manufactured using different processes, in large part because the manufacturing processes of the branded manufacturer may not be publicly disclosed, or may be patent protected. And labels may be different: for example, federal regulations provide for the "carving out" of indications from a generic's label.[8]

The process of seeking and gaining approval of a generic drug in this highly-regulated, highly-involved area is not easy; "[i]n the vast majority of cases, the initial ANDA application is found deficient, requiring the applicant to conduct additional tests or submit additional material."[9] From start to approval, the ANDA process typically takes more than a year and a half, with additional time required before the generic drug can actually be sold.[10] And once approved, generic manufacturers must carefully monitor their products to ensure they are performing equally to the listed reference drug – that

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8. 21 C.F.R. § 314.127(a)(7). *See also* Terry Mahn, *Protecting New Investments in Old Drugs*, Update (The Food & Drug L. Inst.), March/April 2009, at 38, 38-44.

9. David Reiffen & Michael R. Ward, *Generic Drug Industry Dynamics*, 87 The Rev. of Econ. & Stat. 37, 38 (2005).

10. *Id.* (observing "In total, the applicant has to anticipate 2 to 3 years elapsing from the time it begins preparing to enter until it can begin selling a generic drug.").

they are, for example, properly manufactured and indeed bioequivalent to the branded pharmaceutical.

In pursuit of FDA approval and post-market follow-up, generic manufacturers spend millions of dollars each year on research and development ("R&D"), gaining substantial information about the active molecules contained in their products. In 2009, petitioners' *amicus* Teva spent $802 million on generic and innovative R&D.[11] The company emphasized that R&D "efforts are integral to all of our operations," and explained that generic R&D "responsibilities include product formulation, chemical and physical (including shelf-life) testing, stability testing, bioequivalence (absorption and extent), blood level testing, clinical testing, registration and approval."[12] In 2003, *amicus* Apotex boasted that it held "the #1 position in Canada for research and development spending in the pharmaceutical industry," devoting $153 million and 20.4% of total revenue to R&D and beating out the top branded manufacturers both in total R&D spend and R&D spend as a percentage of revenue.[13]

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11. Teva Pharm. Indus. Ltd., Annual Report 2009, at 27 (2010), *available at* http://www.tevapharm.com/pdf/Teva20F2009.pdf ("Teva 2009 Annual Report").

12. *Id.*

13. Press Release, Apotex, Generic Company #1 In Canadian Pharmaceutical Industry for Research & Development Spending, (July 15, 2003), *available at* http://www.apotex.com/PressReleases/20030715-01.asp.

B. Although the Drugs May Differ, Disparities Between Branded and Generic Manufacturers Are Less Stark Than Petitioners and Their *Amici* Suggest

Generic manufacturers share many similarities with their branded counterparts. Indeed, generic manufacturers often enter into agreements with branded manufacturers in the course of launching a generic product and sometimes are even divisions of the same company.

While all must pass FDA muster, generic products come to market in a variety of ways. For example, authorized generics are produced by branded manufacturers and marketed under a private label at generic prices.[14] In other situations, branded and generic manufacturers may enter into agreements allowing the generic to launch with a license from the branded manufacturer, but only after agreeing not to compete for a specified period of time.[15] And some generic products launch in the absence of a

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14. *See, e.g.*, Fed. Trade Comm'n., Authorized Generics: An Interim Report, at Exec. Summary (2009), *available at* http://www.ftc.gov/os/2009/06/index.shtm#24.

15. Fed. Trade Comm'n., Pay-for-Delay: How Drug Company Pay-Offs Cost Consumers Billions, Federal Trade Commission Staff Study, at 3 (Jan. 2010), *available at* www.ftc.gov/os/2010/01/100112payfordelayrpt.pdf; *see also, e.g.*, Prepared Statement of the Federal Trade Commission Before the United States House of Representatives Committee on the Judiciary Subcommittee: Courts and Competition Policy: Oversight of the Federal Trade Commission Bureau of Competition and the Department of Justice Antitrust Division, at 3 (July 27, 2010), *available at* http://www.ftc.gov/os/testimony/100727antitrustoversight.pdf.

brand name counterpart.[16]

The branded and generic industries overlap. Some of the largest "generic" companies are divisions of branded manufacturers: the third- and fifth-largest generic manufacturers, Sandoz and Greenstone, are divisions of investigative drug companies Novartis and Pfizer, respectively.[17] Further, like branded manufacturers, generic manufacturers regularly seek and obtain patents for their products, protecting them against infringement by competitors. For example, in 2009 petitioner Teva's parent, primarily a generic company, derived $2.66 billion

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In 2008, the Federal Trade Commission analyzed the number and types of settlements and agreements between pharmaceutical companies and found that forty-six such agreements between branded and generic manufacturers filed in fiscal year 2008 involved some restriction on a generic manufacturer's ability to market its product. *See* Fed. Trade Comm'n., Agreements Filed with the Federal Trade Commission under the Medicare Prescription Drug, Improvement, and Modernization Act of 2003: Summary of Agreements Filed in FY 2008, at 2-5, fig. III, *available at* http://www.ftc.gov/bc/healthcare/drug/index.htm.

16. *See, e.g.*, 21 U.S.C. § 355(b)(2) (describing "hybrid" applications for drug approval which are neither full NDAs containing safety and efficacy data nor ANDA applications. Products seeking this route of approval use an active pharmaceutical ingredient that the FDA previously has determined is safe and efficacious for its intended use but are modified in some way so that they differ from the original NDA product, *e.g.*, in dosage form, strength, route of administration, changed formulation, dosing regimen, or indication.).

17. Alaric Dearment, *Countdown to 2011: A Big Year for Generics*, Drug Store News, Nov. 14, 2010, *available at* http://www.drugstorenews.com/article/countdown-2011-big-year-generics.

of its $13.9 billion revenue from innovative products.[18]

C. Institutional and Statutory Constructs Promote the Use of Generic Drugs and the Profitability of the Sector

Since passage of Hatch-Waxman in 1984, United States policy has encouraged use of generic medications. Statutory and institutional factors cause generic medications to quickly capture market share and overtake market shares in areas where they compete with branded drugs. This results in the generic industry's significant revenues and profitability.

In 1983, only 35% of the top-selling drugs with expired patents had generic versions available; by 1998, nearly all did.[19] In 1984, prescription drug revenue for branded and generics totaled $21.6 billion and generic drugs accounted for 18.6% of prescriptions.[20] By 2009, total prescription drug revenue had soared to $300 billion and generic drugs accounted for 75% of prescriptions.[21] Overall prescription drug sales, and the generic share of those sales, have

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18. Teva 2009 Annual Report, *supra* n.11, at F-40.

19. Cong. Budget Off., How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry, at xii (1998), *available at* http://www.cbo.gov/ftpdocs/6xx/doc655/pharm.pdf ("CBO 1998").

20. *Id.* at 4, 27. The figure of $21.6 billion is apparently adjusted for inflation as of 1998; the point does not depend on a precise figure.

21. Press Release, IMS Health, IMS Health Reports U.S. Prescription Sales Grew 5.1 Percent in 2009, to $300.3 Billion (April 1, 2010), *available at* http://www.imshealth.com/portal/site/imshealth/menuitem.a46c6d4df3db4b3d88f611019418c22a/?vgnextoid=d690a27e9d5b7210VgnVCM100000ed152ca2RCRD&epsextcurrchannel=1 ("IMS Press Release").

grown considerably in recent years:[22]

Year	Total U.S. sales - branded and generic (billions)[23]	U.S. Sales - generic only (%)[24]	U.S. Sales - generic only (billions)[25]	Total prescriptions (millions)[26]	Total prescriptions that are generic (%)[27]
2003	$219.6	12	$26.4	3,361	51
2004	$239.9	12	$28.8	3,435	53
2005	$247.3	13	$32.1	3,545	57
2006	$270.3	15	$40.5	3,706	61
2007	$280.5	16	$44.9[28]	3,805	63
2008	$285.7	-	-	3,842	-
2009	$300.3	22	$66.1	3,922	75

22. For 2003-2006: Richard Frank, *The Ongoing Regulation of Generic Drugs*, 357 New Eng. J. Med. 1993, 1993-96 (2007). For 2007 and 2008: *Facts at a Glance*, Generic Pharm. Ass'n, http://www.gphaonline.org/about-gpha/about-generics/facts (last visited Feb. 28, 2011) ("GPhA Facts at a Glance"). For 2009: IMS Press Release, *supra* n.21.

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23. For 2003 to 2004: *2007 Top Therapeutic Classes by U.S. Sales*, IMS Health, (2008), http://www.imshealth.com/deployedfiles/imshealth/Global/Content/Document/Top-Line%20Industry%20Data/2007%20Top%20Therapeutic%20Classes%20by%20Sales.pdf. For 2005 to 2009: *Top Therapeutic Classes by U.S. Sales*, IMS Health, (2010), http://www.imshealth.com/deployedfiles/imshealth/Global/Content/StaticFile/Top_Line_Data/Top%20Therapy%20Classes%20by%20U.S.Sales.pdf.

24. For 2003 to 2007: Frank, *supra* n.22, at 1994. For 2009: Natasha Singer, *Deals to Restrain Generic Drugs Face a Ban*, N.Y. Times, Jan. 13, 2010, at B1.

25. Dollar figures for "U.S. Sales - generic only" are calculated by taking the given percentage of "Total U.S. sales - branded and generic."

26. For 2003 to 2004: *2007 Top Therapeutic Classes by U.S. Dispensed Prescriptions*, IMS Health, (2008), http://www.imshealth.com/deployedfiles/imshealth/Global/Content/Document/Top-Line%20Industry%20Data/2007%20Top%20Therapeutic%20Classes%20by%20RXs.pdf. For 2005 to 2009: *Top Therapeutic Classes by U.S. Dispensed Prescription*, IMS Health, (April 6, 2010), http://www.imshealth.com/deployedfiles/imshealth/Global/Content/StaticFile/Top_Line_Data/Top%20Therapy%20Classes%20by%20U.S.RXs.pdf.

27. For 2003 to 2007: Frank, *supra* n.22. For 2009: IMS Press Release, *supra* n.21.

28. Our calculated figure may be low; other reports put generic industry revenue in 2007 at $58.5 billion. GPhA Facts at a Glance, *supra* n.22.

Indeed, just since 2003, the share of total prescriptions filled by generic manufacturers has grown from 51% to 75%, with generic sales expanding from $26.4 billion to $66.1 billion. Generic drug sales in some years fully account for the growth in medication spending: "[t]he total number of generic prescriptions dispensed increased 5.9 percent in 2009, while the number of branded prescriptions dispensed *declined* 7.6 percent."[29] And the generic industry will likely continue to grow as the United States seeks to limit medication costs.[30]

Where they do compete with branded drugs, generic drugs quickly capture the majority of sales. More than 90% of prescriptions for "multiple-source" drugs (meaning they are available in branded and generic forms) are filled by generics.[31] The speed of market share capture by generic drugs appears to be increasing: in a sample of drugs losing patent protection between 1991 and 1993, generics on average held a 44% market share after one year;[32] by 2008, generic versions could capture "as much as 86 to 97 percent of the market within the first month."[33]

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29. IMS Press Release, *supra* n.21 (emphasis added).

30. *See generally, e.g.*, U.S. Dep't Health & Hum. Serv., ASPE Issue Brief, Expanding Use of Generic Drugs (Dec. 1, 2010), *available at* http://aspe.hhs.gov/sp/reports/2010/GenericDrugs/ib.pdf ("ASPE Issue Brief").

31. Cong. Budget Off., Effects of Using Generic Drugs on Medicare's Prescription Drug Spending, at 7 (2010), *available at* http://www.cbo.gov/ftpdocs/118xx/doc11838/09-15-PrescriptionDrugs.pdf.

32. CBO 1998, *supra* n.19, at 28.

33. Protecting Consumer Access to Generic Drugs Act of 2009: Hearing on H.R. 1706 Before the U.S. House of Representatives

As a result of this generic competition, branded manufacturers often cease production of out-of-patent drugs entirely. In 2009, out of a universe of 4,318 unique drug molecules with active sales volume tracked by IMS Health, a leading aggregator of pharmaceutical sales and prescription data, 32% were sold solely as generics.[34] Our own analysis of FDA data indicates that out of 4,653 approved drugs with distinct ingredients, delivery routes, and strengths, more than half – 2,438 – are available in generic form. Of those, 1,062 are available *solely* in generic form; the only available versions of the drug received ANDA approval.[35]

Subcommittee on Commerce, Trade and Consumer Protection, of the Committee on Energy and Commerce 8 (March 31, 2009) (prepared statement of Diane E. Bieri, Exec. VP and Gen. Coun., Pharm. Research & Mfrs. of Am.).

34. Generic Pharm. Ass'n, Savings Achieved Through the Use of Generic Pharmaceuticals 2000-2009, at 7 (2010), *available at* http://www.gphaonline.org/sites/default/files/GPhA%20Savings%20Study%20Book%20Updated%20Web%20FINAL%20Jul23%2010_0.pdf ("GPhA, Savings Achieved 2000-2009").

35. We base this analysis on the FDA's "Orange Book" database. The FDA's Orange Book lists approved drug products with therapeutic equivalence evaluations, all of which have been approved under Section 505 of the Federal Food, Drug, and Cosmetic Act. *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations*, U.S. Food & Drug Admin., http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm (last visited Feb. 26, 2011). We filtered the database to include only prescription medications; grouped individual products having a unique combination of ingredients, delivery routes, and strengths; and counted what portion of the groups contained NDA products, ANDA products, or both. *Electronic Orange Book (EOB) Query Data Files*, U.S. Food & Drug Admin., http://www.fda.gov/Drugs/InformationOnDrugs/ucm129689.htm (last visited Jan. 11, 2011).

Several factors influence generic manufacturers' ability to capture market share. Since passage of Hatch-Waxman, every state has adopted substitution laws that either require or permit pharmacies to substitute generic equivalents for branded prescriptions unless the prescribing physician has specifically ordered otherwise.[36] Even beyond this, pharmacies have an incentive to substitute generic drugs if possible. When a drug becomes newly available as a generic, federal reimbursement rules and the industry pricing structure typically mean pharmacies can earn a higher markup on the generic option than the branded one.[37] In the private market, insurers may offer direct incentives to pharmacies to substitute cheaper generic products for more expensive branded ones.[38] As a result of these incentives, one recent study found no significant difference in substitution rates between "permissive" and "mandatory" substitution states.[39]

Consumers are also incentivized to select generic medications. Many insurers require lower consumer

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36. *See* Judith K. Hellerstein, *The Importance of the Physician in the Generic versus Trade-Name Prescription Decision*, 29 RAND J. Econ. 108, 109 (1998); ASPE Issue Brief, *supra* n.30, 7-8.

37. *See* Cong. Budget Office, Medicaid's Reimbursements to Pharmacies for Prescription Drugs, at 4 (2004), *available at* http://www.cbo.gov/ftpdocs/60xx/doc6038/12-16-Medicaid.pdf.

38. Helene L. Lipton et al., *Pharmacy Benefit Management Companies: Dimensions of Performance*, 20 Ann. Rev. Pub. Health 361 (1999).

39. ASPE Issue Brief, *supra* n.30, at 8 (citing William H. Shrank et al., *State Generic Substitution Laws Can Lower Drug Outlays Under Medicaid*, 29 Health Affairs 1383 (2010)).

copayments for generics than branded drugs to encourage consumers to request a generic option.[40] Federal agencies routinely investigate ways to encourage consumer adoption of generic medication.[41] And according to petitioners' *amicus* Generic Pharmaceutical Association ("GPhA"), both the FDA itself and the generic industry spend millions of dollars each year encouraging customers to trust generic drugs in place of their branded counterparts.[42]

All of this combines to help many generic manufacturers earn above-average profit margins. Profit margins for the top fifty industries averaged 4.9% in 2008;[43] concurrently, petitioners and their *amici* saw profits of 12-25%, some of which even topped the pharmaceutical industry's 19.3% profit margin without incurring the risk undertaken by branded manufacturers in researching potential new drugs that may never come to market.

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40. *See* Geoffrey F. Joyce et al., *Employer Drug Benefit Plans and Spending on Prescription Drugs*, 288 J. Am. Med. Ass'n 1733, 1733-34 (2002); Haiden A. Huskamp et al., *The Effect of Incentive-based Formularies on Prescription-Drug Utilization and Spending*, 349 New Eng. J. Med. 2224, 2225 (2003).

41. *See generally* ASPE Issue Brief, *supra* n.30.

42. Brief of the Generic Pharm. Ass'n as Amicus Curiae in Support of Petitioners at 2-3, *Pliva, Inc., et al. v. Mensing* (No. 09-993) ("GPhA Brief").

43. *Top Industries: Most Profitable*, Fortune (May 4, 2009), http://money.cnn.com/magazines/fortune/fortune500/2009/performers/industries/profits/.

Company	Last Available Year	Revenue	Net Income	Calculated Profit Margin
PLIVA, Inc.[44]	2007	6,061,978 HRK (Croatian Kuna)	731,934 HRK	12.1%
Teva Pharmaceuticals Industries Ltd.[45]	2009	$13.9 billion	$2 billion	14.4%
Actavis[46]	2009	1.7 billion euros	300 million euros (estimated earnings before interest, tax, depreciation and amortisation)	17.6%
Morton Grove Pharmaceuticals Inc.[47]	2009	2,959.41 million rupees	751.20 million rupees	25.4%

44. PLIVA, Annual Report 2007, at 4 (2008), *available at* http://www.pliva.com/newsattach/2246/2007%20Annual%20Report%20EN%20FINAL.pdf.

45. Teva 2009 Annual Report, *supra* n.11, at 2.

46. Ben Hirschler & Quentin Webb, *Actavis Sees Record Year, No Rush to Sell*, Reuters, Sept. 30, 2010, *available at* http://www.forexpros.com/news/financial-news/interview-update-1-actavis-sees-record-year,-no-rush-to-sell-163724 (last visited Feb. 28, 2011). Because Actavis is not publicly traded, public estimates of its profit margin are approximate.

47. Wockhardt Unlimited, Annual Report 2009-10, at 73 (2010), *available at* http://www.wockhardt.com/pdf/investor/annual/NotestoAccounts_2009.pdf.

In sum, generic manufacturers have enjoyed considerable recent growth in revenue and profit as regulatory and institutional factors grant them an increasing share of the prescription medication market.

II. GENERIC MANUFACTURERS OFTEN LEARN OF SAFETY RISKS BEFORE THE FDA OR OTHER HEALTHCARE STAKEHOLDERS

A. Generic Manufacturers Must Investigate and Report Safety Risks

"[I]t has remained a central premise of federal drug regulation that the manufacturer bears responsibility for... ensuring that its warnings remain adequate as long as the drug is on the market."[48] In large part, this responsibility derives from the fact that pharmaceutical manufacturers, whether branded or generic, are often better positioned than the FDA or consumers to learn of, and warn about, such risks.

While not identical to the post-approval requirements imposed on NDA holders, generic manufacturers marketing under an approved ANDA also face post-approval reporting requirements regarding the safety of their products and the need to monitor ongoing bioequivalency. These manufacturers must "develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences ["ADEs"] to FDA."[49] Generic manufacturers must report all ADEs to the FDA, either in periodic reports or, in the

48. *Wyeth v. Levine*, 129 S. Ct. 1187, 1197-98 (U.S. 2009).

49. 21 C.F.R. § 314.80(b) (made applicable to generic companies by 21 C.F.R. § 314.98).

case of "serious and unexpected" ADEs, within fifteen days of learning of them.[50] "Serious and unexpected" ADEs that "may jeopardize the patient or subject" require "prompt[] investigat[ion]" and submission of follow-up reports to the FDA by the generic manufacturer.[51]

By 1998, approximately 90% of ADE reports came from manufacturers;[52] these reports are more valuable than ones filed directly with the FDA, because they "leverage[] the firm's resources in identifying, assessing, and following up on reports of drug injury."[53] Follow-up from ADEs can lead to the dissemination of important safety information. For example, *amicus* Teva engaged in a nationwide recall of its anesthesia product propofol in 2009 after receiving and investigating information from ADEs.[54]

Put differently, generic manufacturers already face post-reporting requirements. The imposition of potential

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50. *Id.* at § 314.80(c)(1)(i), (c)(2).

51. *Id.* at § 314.80(a), (c)(1)(ii).

52. *See* Vaccine Adverse Event Reporting System: Hearing Before the House Com. on Gov't Reform, (May 27, 1999) (prepared statement by Joseph A. Levitt, Dir., Ctr. for Food Safety and Applied Nutrition, Food & Drug Admin.), *available at* http://www.fda.gov/NewsEvents/Testimony/ucm115054.htm.

53. *Id.*

54. Press Release, Teva, Teva Pharmaceuticals USA Issues a Voluntary User-Level Nationwide Recall of Propofol Injectable Emulsion 10 mg/mL 100 mL Vials, Lot Numbers 31305429B and 31305430B (July 16, 2009), *available at* http://www.fda.gov/Safety/Recalls/ArchiveRecalls/2009/ucm172474.htm.

liability through state-law failure-to-warn suits simply provides added incentive to fulfill these obligations.

B. The FDA Cannot Track Safety Data for All Approved Drugs

Writing in the context of litigation against a branded pharmaceutical manufacturer, this Court observed in *Wyeth v. Levine* that "[t]he FDA has limited resources to monitor the 11,000 drugs on the market, and manufacturers have superior access to information about their drugs, especially in the postmarketing phase as new risks emerge."[55] A similar imbalance in resources and knowledge of post-approval risk information exists between the FDA and a generic manufacturer; state law should be allowed to impose a duty on generic manufacturers to disclose known risk information.

The FDA possesses a limited ability to monitor generic medications for emerging safety problems. The universe of approved drugs that must be monitored by the FDA's limited resources is large and grows daily; as this Court noted, there are more than 11,000 currently-approved prescription medications,[56] of which 4,318 separate molecules have active sales volume.[57] New medications are typically approved based on a small number of studies in a modest number of subjects. Such limited testing permits important new products to come to

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55. 129 S. Ct. at 1202 (internal citation omitted).

56. *See id.*

57. *See* GPhA, Savings Achieved 2000-2009, *supra* n.34, at 7.

market relatively quickly[58] but also means that when the FDA approves a drug, it "cannot fully certify its ongoing safety."[59] Instead, the FDA relies on postmarketing data from manufacturers to refine the safety profile of a drug.

But the FDA has long-acknowledged deficiencies in its ability to acquire post-approval drug risk information. The FDA had no more that 211 employees in 2009 in its Office of Surveillance and Epidemiology, which is responsible for evaluating and monitoring ongoing risks for all drugs,[60] and total FDA funding for postmarketing drug safety reached only $139 million in fiscal year 2008.[61] In fact, the Government Accountability Office placed the FDA's drug safety program on its watchlist of high-risk areas requiring attention by Congress and the executive branch, stating in February 2011:

> Although improvements have been made, long-standing concerns remain regarding the

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58. Should FDA Drug and Medical Device Regulation Bar State Liability Claims?: Hearing Before H. Comm., on Oversight and Government Reform, 110th Cong., Ser. No. 110-212, at 30 (May 14, 2008) (statement of Aaron S. Kesselheim, Harvard Med. Sch.).

59. *Id. See, e.g., A Guide to Drug Safety Terms at FDA*, U.S. Food & Drug Admin., (Feb. 28, 2011), http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm107970.htm ("[E]ven with a rigorous evaluation process, some safety problems surface only after a drug has been on the market and has been used in a broader population,").

60. U.S. Gov't Accountability Off., GAO-10-68, Drug Safety: FDA Has Begun Efforts to Enhance Postmarket Safety, but Additional Actions Are Needed, at 1, n.75 (2009) ("GAO-10-68").

61. *Id.* at 14.

> effectiveness of FDA's postmarket oversight. FDA staff have expressed concern about their ability to meet a growing postmarket workload, with some maintaining that their premarket responsibilities are considered a higher priority. FDA is also encountering technological and staffing issues that limit its capacity to conduct drug safety studies.[62]

Problems with the FDA's postmarketing drug safety monitoring have been reported for over thirty years.[63] In a 2006 report, the GAO observed that the "FDA's postmarket drug safety decision-making process has been limited by a lack of clarity, insufficient oversight by management, and data constraints."[64] Fiscal constraints are another important limitation, with a large majority of the FDA's drug safety budget earmarked for premarketing rather than postmarketing efforts, and a majority of FDA doctors and scientists believing that the agency lacks sufficient funds to do its job.[65] Congress expanded the FDA's post-marketing budget in 2007 but simultaneously expanded the Agency's post-approval surveillance duties as well,

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62. U.S. Gov't. Accountability Off., GAO-11-278, High-Risk Series: An Update 116-17 (February 2011).

63. GAO-10-68, *supra* n.60, at 39.

64. U.S. Gov't. Accountability Off., GAO-06-402, Drug Safety: Improvement Needed in FDA's Postmarket Decision-making and Oversight Process 18 (2006).

65. David A. Kessler & David C. Vladeck, *A Critical Examination of the FDA's Efforts To Preempt Failure-To-Warn Claims*, 96 Geo. L.J. 461, 484-85 (2008). *See also* GAO-10-68, *supra* n.60, at 2, 31-34.

leaving unchanged the problem of inadequate funding.[66] Following the increase in funding and postmarketing duties, the GAO opined in 2009 that "it is not yet clear if or when FDA's decision-making process will be substantially improved as a result of its efforts."[67]

C. Many Risks Do Not Emerge Until After Patent Expiration for the Branded Drug

Under the system proposed by petitioners' *amici*, branded manufacturers and the FDA are solely responsible for developing drugs, monitoring them for emerging safety concerns, reporting safety signals, and proposing label changes; generic manufacturers need only follow their directions. But (1) an increasing number of drugs have no branded company to monitor them; (2) many long-term risks do not emerge until after a drug goes generic; and (3) some risks arise spontaneously when a product is manufactured by a generic company, including contamination and other manufacturing problems as well as safety concerns resulting from differences between the branded and generic products.

Petitioners' *amici* suggest that the safety of all drugs will be maintained through monitoring and reporting required of NDA holders:

> Each applicant having an approved application under § 314.50 or, in the case of a 505(b)(2) application, an effective approved application,

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66. Kessler & Vladeck, *supra*, at 485-86; *see* GAO-10-68, *supra* n.60, at 13.

67. GAO-10-68, *supra* n.60, at 39.

> shall promptly review all adverse drug experience information obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers.[68]

Whatever optimistic view one might hold for branded manufacturer compliance with existing regulations, the plain economic fact is that a growing number of drug products distributed in the U.S. have no corresponding approved application under § 314.50: out of 2,438 distinct drugs available as generics through ANDA applications, nearly half are available solely in that form—any approved applications under § 314.50 have been withdrawn.[69] Petitioners and their *amici* would leave an entire segment of distributed drug products without any surveillance.

Further, branded drugs are frequently approved after only short-term safety studies have been conducted and the long-term effects of a drug typically are not known or reported for many years. Ongoing monitoring for emerging side effects is thus an important tool to ensure drug safety, even in drugs that have lost patent protection. For example, Neurontin, approved for use in treating epilepsy, entered the market in 1996 and lost patent protection in 2004. During that time, Neurontin sales exceeded $10 billion and in 2003, Neurontin was one

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68. 21 C.F.R. § 314.80(b).

69. *Supra* n.35 and accompanying text.

of the most-prescribed drugs in the United States. Risks of suicidal ideation associated with Neurontin and generic versions of the drug emerged late in the day and led to a label change, warning of suicidality, in 2009, five years after generics entered the market.

Metoclopramide, a drug at issue here, is another example. First marketed as Reglan in 1979, the drug was available in generic form by the mid-1980s. New risk information continued to emerge, causing significant label changes for safety issues in 2004 and 2009, more than twenty-five years after its launch.

Recent news about the analgesic Darvon is apt. Darvon, known generically as propoxyphene, was approved for use in 1957 for use in treating mild to moderate pain. In November 2010, more than forty years after approval, the FDA requested that all manufacturers of propoxyphene remove the drug from market after determining the risks of severe cardiac side effects outweighed the benefits of the drug.[70]

"Off-label" uses of a drug increase the possibility of new side effects. For example, in 1981, the FDA approved the antidepressant trazadone hydrochloride for the treatment of depression under the brand name Desyrel.[71]

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70. *See, e.g.*, Duff Wilson, *Darvon Pulled From Market by F.D.A.*, N.Y. Times, (Nov. 19, 2010), http://prescriptions.blogs.nytimes.com/2010/11/19/darvon-pulled-from-market-by-f-d-a/ (last visited Feb. 28, 2011).

71. *See Label and Approval History for Desyrel*, Drugs @ FDA, U.S. Food & Drug Admin., http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist (last visited Feb. 28, 2011).

Desyrel lost patent protection in the mid 1980s. By the late 1980s, physicians prescribed trazodone off-label with increasing frequency to treat insomnia. As off-label use of trazodone increased, new side effects emerged, including the risk of excessive sedation when used for insomnia with fluoxetine, a selective serotonin reuptake inhibitor (such as Prozac).[72]

Some risks can arise as a result of differences between the branded and generic versions of a drug. In 2006, the FDA approved *amicus* Teva's ANDA for Budeprion XL, a generic version of the antidepressant Wellbutrin XL. Scores of patients reported loss of effect and new onset or worsening of side effects when switching from branded Wellbutrin XL to generic Budeprion XL, leading to an investigation by the FDA into whether differences between the drugs in the manufacturing and rate of chemical release and absorption caused safety risks for Budeprion XL not seen in Wellbutrin XL.[73]

The regime proposed by the petitioners is therefore one in which, for nearly half the drugs they produce, the FDA is solely responsible for monitoring the medical literature and ADEs for emerging safety concerns. Under this scheme, neither generic manufacturers nor any other private party has a duty to evaluate the ongoing safety of

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72. Alan Metz and Richard I. Shader, *Adverse Interactions Encountered When Using Trazodone to Treat Insomnia Associated with Fluoxetine*, 5 Int'l. Clinical Psychopharmacology 191 (1990).

73. *E.g.*, *Review of Therapeutic Equivalence Generic Buproprion XL 300mg and Wellbutrin XL 300mg*, U.S. Food & Drug Admin., http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm153270.htm (last visited Feb. 27, 2011).

their products or report known risks, and patients have no recourse if the generic manufacturers unreasonably ignore information that could have prevented personal injury. Such a reading of federal law and regulation is not one that Congress or the FDA would likely have selected, or one that should be adopted lightly.

III. GENERIC MANUFACTURERS PRESENT NO EVIDENCE THAT A DUTY TO WARN CONFLICTS WITH, OR WILL CRIPPLE, THE HATCH-WAXMAN SCHEME

Petitioners and their *amici* argue that compliance with duties to report safety information would undo all of the benefits generated by Hatch-Waxman. To the contrary, failure to hold generic manufacturers accountable for non-disclosure of known risks associated with their products would create important differences between branded and generic drugs that are likely to be exploited in marketing campaigns and that may result in a turning away from generic drugs by physicians and consumers, not to mention a rethinking of state generic substitution laws.

Petitioners' *amici* suggest that requiring generic manufacturers to monitor the safety of their products will "wipe out" more than $100 billion per year in savings under the Hatch-Waxman scheme.[74] They make no attempt to estimate the actual costs to generic manufacturers of reporting known health risks, or of monitoring widely-available public information about a generic drug. Nor do they explain why doing so would be so costly as to seriously undermine the savings from the use of generic rather than branded drugs.

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74. *See* GPhA Brief, *supra* n.42, at 3.

This case, and others like it, seeks to impose on generic manufacturers only the most minimal duties of surveillance and disclosure of risk information. No one questions the reasonableness of adopting the labels used by branded companies, approved by the FDA, and consistent with medical literature at the time a drug loses patent protection. But to comply with their ongoing duties, generic manufacturers must act on information that becomes reasonably available to them – ADEs and published medical literature – to ensure that their product labels provide adequate notice of safety requirements.

Petitioners' assertion boils down to this: because Congress intended their products to be affordable, it must have intended to exempt generic manufacturers from all economic burdens associated with the manufacture and distribution of generic drugs, including the cost of reporting available information about their products to ensure that product use remains safe and labels are kept up to date. This is not so. The generic industry remains subject to a wide range of laws that impose costs of doing business, including state wage and hour laws, state discrimination laws, and state torts for negligent manufacture. It has achieved success without exemption from those laws, and has demonstrated no real need for exemption from the claims at issue here.

Economics teaches us that the cost of accidents is lessened where society imposes such costs on "the 'cheapest cost avoider' or [the actor] who is in the best position to make the cost-benefit analysis between accident costs and accident avoidance costs and to act

on that decision once it is made."[75] This Court's finding in *Wyeth v. Levine* recognized and upheld this teaching, finding manufacturers of pharmaceuticals "have superior access to information about their drugs, especially in the postmarketing phase as new risks emerge,"[76] and that "state-law remedies further consumer protection by motivating manufacturers to produce safe and effective drugs and to give adequate warnings."[77] Petitioners and their *amici* ask this Court to reject this notion only two years later, setting up an entirely different standard for generic manufacturers than their branded counterparts.

The decision to hold generic manufacturers to the same state law standard as branded manufacturers directly serves Congress's intent to create a market of generic drugs equivalent in value to their branded counterparts. For the generic market to succeed, generic drugs must have equal value to branded drugs; in economic terms, they must be "perfect substitutes," and in safety terms, the requirements for disclosure of risk must be equal to that applied to branded drugs A holding that product liability claims are preempted against generic manufacturers but not against branded manufacturers undercuts these goals.

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75. *Beshada v. Johns-Manville Prods. Corp.*, 447 A.2d 539, 548 (N.J. 1982) (*citing* Guido Calabresi & Jon T. Hirschoff, *Toward a Test for Strict Liability in Torts*, 81 Yale L.J. 1055 (1972)); *see generally* Robert L. Rabin, *Reassessing Regulatory Compliance*, 88 Geo. L.J. 2049, 2071 (2000).

76. 129 S. Ct. at 1202.

77. *Id.* at 1200.

In the marketplace, critical to the value equation for any product is the consumer's recourse in the event a product is defective. A product sold "as is" is less valuable than one sold with the implied warranties of fitness and merchantability. A product sold without waiver of personal injury claims resulting from any defect is more valuable than one sold with waiver. Similarly, a product sold without preemption of state tort claims is more valuable than one sold with preemption. Taking the case at hand as an example, patients whose prescriptions were filled with name-brand Reglan may be able to recover under state law if they suffer tardive dyskinesia because their medication was defectively labeled. Patients whose prescriptions were filled with identically labeled generic metoclopramide will not have recourse to any recovery.

The fact that a broad class of patients suffered the misfortune of having prescriptions filled with generics, as encouraged or often required by state substitution laws, would not go unnoticed in the marketplace – if for no other reason than because branded manufacturers would have a strong incentive to publicize that information. The bifurcated scheme proposed by petitioners and their *amici* will create a hierarchical distinction between branded drugs and generic therapeutic substitutions by mandating substantially greater safety monitoring for branded drugs and, from a safety point of view, an inferior class of solely generic drugs. A doctor choosing between therapeutic substitutes will therefore have a practical incentive to select the branded drug knowing its patent holder will actively monitor it for health risks (and that if there is a failure to do so, the patient will have recourse), thereby undercutting Congress's goal to promote substitution of generic equivalents. This Court recently determined

state-law failure-to-warn suits concerning branded drugs are not preempted; finding preemption for similar suits concerning generic drugs places actually places generic drugs at a competitive disadvantage in the healthcare marketplace.

In sum, petitioners and their *amici* present no evidence that state tort claims must be preempted to preserve the viability of the generic market. A finding of preemption would in fact undercut the purposes of Hatch-Waxman, as well as the confidence physicians and consumers have in generic products, by creating a meaningful difference in the value of generic and branded drugs where previously none existed.

IV. STATE TORT LIABILITY ENSURES THE INCENTIVES OF GENERIC MANUFACTURERS, LIKE THEIR BRANDED COUNTERPARTS, ARE ALIGNED WITH CONSUMERS

The contributions of tort law to product safety were recognized early on by leading thinkers of the law and economics movement. The safety and efficiency benefits of state-law failure-to-warn suits are precipitated by a nuanced array of economic and structural forces, but all those forces are tied together by two fundamental concepts: incentives and information. The recourse provided by state failure to-warn suits helps align producer incentives with consumer safety concerns and ensure that consumers have optimal information so that market transactions are more apt to be based on mutually beneficial exchanges between consumers and producers.

A. Failure-to-Warn Litigation Promotes Safety by Encouraging Drug Manufacturers to Respond to Risks

Both branded and generic manufacturers share the need to be incentivized beyond the federal regulatory machinery to report known safety risks or signals of their products. State tort suits provide the incentives that complement the FDA, a deterrence mechanism that federal agencies like the FDA cannot replicate. The availability of state failure-to-warn litigation helps protect consumers when harmful consequences become apparent regarding drugs that have already been approved by the FDA. When such information becomes apparent to manufacturers and not the FDA, as is usual, manufacturers may not act appropriately with that information.

Manufacturers often continue to distribute their products for many years while denying serious safety risks or downplaying emerging safety concerns.[78] That conduct occurs because providing new safety information quickly and accurately to the FDA may cause the Agency to recommend adding new warnings to the label, or to remove the drug from the market altogether, reducing (or eliminating) use of the product as well as manufacturer profits. Even under the current system, there is evidence

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78. *See* Bruce M. Psaty & Richard A. Konmal, *Reporting Mortality Findings in Trials of Rofecoxib for Alzheimer Disease or Cognitive Impairment: A Case Study Based on Documents from Rofecoxib Litigation*, 299 J. Am. Med. Ass'n 1813, 1813-17 (2008); Bruce M. Psaty et al., *Potential for Conflict of Interest in the Evaluation of Suspected Adverse Drug Reactions: Use of Cerivastatin and Risk of Rhabdomyolysis*, 292 J. Am. Med. Ass'n 2622, 2626-30 (2004).

that some drug manufacturers have attempted to hide information from the FDA to get approval to market their drugs.[79]

State failure-to-warn litigation provides substantial penalties for manufacturers' decisions to hide or downplay reports of safety issues that emerge after a product reaches the market. Potential damage awards provide drug manufacturers with a strong incentive to expeditiously provide full and clear information to physicians and the FDA that otherwise may not come to light. Without such litigation, drug manufacturers would have a stronger incentive to act in their immediate financial interest and be less forthcoming in providing emerging safety-related data and the vast majority of consumers would have no remedy or recourse in the face of injury as a result of drug manufacturers' failure to disclose known risk information.

Further, state failure-to-warn suits encourage drug manufacturers to work with the FDA to ensure that labels accurately reflect the risks associated with a given treatment. The overwhelming incentive in the absence of state tort liability would be to refrain from proposing label changes under FDA regulations, even though they have the right and duty to propose such changes and even if they have a clear understanding that such changes are necessary to protect patient health.

Reducing the potential cost of concealing information (which would occur if state tort liability were removed)

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79. *See, e.g., In re Baycol Prods. Litig.*, 218 F.R.D. 197, 201-02 (D. Minn. 2003); *In re W. Va. Rezulin Litig.*, 585 S.E.2d 52, 58-59 (W. Va. 2003).

would encourage drug manufacturers to withhold critical safety information more often. Failure-to-warn litigation thus encourages manufacturers to market their products accurately and fairly. The net effect of this complementary arrangement is the promotion of full and accurate knowledge about drug risks and the minimization of misstatements or error in drug labeling. A significant literature chronicles the social welfare benefits of dual regulation of risky technologies,[80] noting, for example, that "[t]he common law system's independence and private incentives to challenge the status quo are particularly valuable antidotes to complacency and ineffective regulation."[81] Accordingly, state-law failure-to-warn litigation serves as a valuable complement to FDA regulation.

B. Harnessing the Forces of Decentralization, Failure-to-Warn Litigation Expedites the Diffusion of New and Potentially Vital Information on Emerging Drug Risks

State tort liability suits serve an essential role in facilitating the rapid transmission of information about drugs' properties. Given the decentralized nature of

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80. *See generally* C.F.Larry Heimann, *Acceptable Risks: Politics, Policy, and Risky Technologies* (1997); Jonathan Bendor, *Parallel Systems: Redundancy in Government* (1985); Michael M. Ting, *A Strategic Theory of Bureaucratic Redundancy*, 47 Am. J. Pol. Sci. 274 (2003); Martin Landau, *Redundancy, Rationality, and the Problem of Duplication and Overlap*, 29 Pub. Rev. 346 (1969).

81. William W. Buzbee, *Asymmetrical Regulation: Risk, Preemption, and the Floor/Ceiling Distinction*, 82 N.Y.U. L. Rev. 1547, 1578 (2007).

the court system, civil tort trials can help reveal the unexpected effects of drugs after they have been approved by the FDA, and even after the branded manufacturer has left the market, by providing individuals with local recourse. Litigation brought by individual patients can help uncover previously unavailable data on adverse effects, questionable practices by manufacturers, and flaws in regulatory systems.[82]

Forcing generic manufacturers to report known safety risk or signal information places drug-wide labeling issues under the microscope of the adversarial system and at the FDA. The immense value of the adversarial system in gathering information that even a centralized body of experts might miss is a philosophical pillar of the U.S. court system.[83]

The court system harnesses the power of market forces to catalyze the dissemination of information. Failure-to-warn suits give lawyers an economic incentive to gather information about safety risks or signals which might be known to drug manufacturers but which have not yet been acted upon by national regulatory bodies. Conversely, the nontrivial costs of bringing a failure-to-warn suit acts as an additional filter on the legitimacy of the cases brought before the court: plaintiffs' attorneys will not recoup their investment if they undertake cases

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82. Aaron S. Kesselheim & Jerry Avorn, *The Role of Litigation in Defining Drug Risks*, 297 J. Am. Med. Ass'n 308, 308-11 (2007).

83. *See, e.g.*, David Bernstein, *Expert Witnesses, Adversarial Bias, and the (Partial) Failure of the Daubert Revolution*, 93 Iowa L. Rev. 451, 457 n.28 (2008).

without a reasonable hope of success. Similarly, FDA decisions and pronouncements can also play a significant role in juries' evaluation of failure-to-warn cases.[84]

84. Kessler & Vladeck, *supra* n.65, at 477 (noting that a "drug company would have a powerful defense" when it is "able to argue to the jury that it complied with applicable FDA requirements and that the plaintiff is complaining about the absence of a warning the FDA had rejected").

CONCLUSION

Given the potential ambiguity and bias inherent in drug risk assessment, the well-documented problems with manufacturers' reporting of adverse events to the FDA, and the Agency's limited capacity to analyze the safety data it receives, state failure-to-warn suits are necessary to supplement the FDA's regulatory mission. Generic manufacturers have ample scientific and financial resources with which to fulfill the reasonable demands of product liability in state court. Continued tort liability is essential to preserve the alignment of manufacturers' and consumers' interest in full disclosure of evolving risk information. For these reasons and those in the respondents' brief, the Court should affirm the judgment of the lower courts.

Respectfully submitted,

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AMICUS CURIAE BRIEF

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PLIVA, INC., et al.,
Petitioners,
v.
GLADYS MENSING,
Respondent.

ACTAVIS ELIZABETH LLC,
Petitioner,
v.
GLADYS MENSING,
Respondent.

ACTAVIS, INC.,
Petitioner,
v.
JULIE DEMAHY,
Respondent.

On Writs Of Certiorari To The United States Courts Of Appeals For The Eighth And Fifth Circuits

BRIEF OF AMICI CURIAE STATES OF MINNESOTA, LOUISIANA, ALABAMA, ALASKA, ARIZONA, ARKANSAS, CALIFORNIA, COLORADO, CONNECTICUT, DELAWARE, HAWAII, IDAHO, ILLINOIS, INDIANA, IOWA, KENTUCKY, MAINE, MARYLAND, MASSACHUSETTS, MISSISSIPPI, MISSOURI, MONTANA, NEBRASKA, NEVADA, NEW HAMPSHIRE, NEW MEXICO, NEW YORK, NORTH CAROLINA, NORTH DAKOTA, OHIO, OKLAHOMA, PENNSYLVANIA, RHODE ISLAND, SOUTH CAROLINA, SOUTH DAKOTA, TENNESSEE, UTAH, VERMONT, WASHINGTON, WEST VIRGINIA, WISCONSIN, WYOMING, AND THE DISTRICT OF COLUMBIA IN SUPPORT OF RESPONDENTS

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INTEREST OF THE AMICI CURIAE

The amici states have two principal interests at stake in these consolidated cases. First, as independent sovereigns in our federal system, the states have a strong interest in the Court continuing to apply the doctrine of implied preemption in a way that rarely negates state law. This is the approach the Court recently followed in *Wyeth v. Levine*, 129 S. Ct. 1187 (2009), which held that the Federal Food, Drug, and Cosmetic Act does not impliedly preempt all state tort failure-to-warn claims against brand-name drug manufacturers.

Second, the amici states have a significant public policy interest in the Court reaching the same result here for generic drugs as it did for brand-name drugs in *Levine*. Consumer protection, public health, and state budgets would be undermined if generic drug manufacturers were shielded from all state tort claims of this kind even when they sell drugs knowing that the label does not contain adequate warnings. Implied preemption would: (1) deny injured consumers of generic drugs a remedy; (2) treat similarly-situated consumers differently; (3) eliminate a significant incentive for generic manufacturers to ensure the adequacy of warnings; (4) leave uncompensated damages caused by generic drugs to be borne by state taxpayers who help finance Medicaid and other health-care programs; and (5) be inconsistent with state laws that encourage substitution of generics for brand-name drugs.

In short, the amici states support a constrained application of implied preemption, with the result here that manufacturers are not allowed to sell inadequately labeled generic drugs with impunity.

SUMMARY OF ARGUMENT

In *Wyeth v. Levine*, 129 S. Ct. 1187 (2009), the Court held that the Federal Food, Drug, and Cosmetic Act (FDCA) does not impliedly preempt all state tort failure-to-warn claims against brand-name drug manufacturers. The result should be no different when generic manufacturers are sued, especially since generics are now used to fill 70% of prescriptions. *Levine* stressed that manufacturers bear primary responsibility for drug labeling and that state tort law offers additional protection that is complementary to regulation under the FDCA.

Notwithstanding *Levine*, the generic manufacturers argue that state tort suits are barred in their entirety by implied preemption. They invoke the same theories of impossibility and frustration preemption that failed in *Levine*. Neither of these arguments overcomes the presumption against preemption, which requires a showing that Congress clearly intended to negate state law.

1. Federal law does not make it physically impossible for generic manufacturers to satisfy their state tort duty to adequately warn consumers of serious risks. Although there is disagreement over

the procedures available for generic manufacturers to revise a drug's labeling, it is undisputed that they can request and obtain Food and Drug Administration (FDA) approval to add a new label warning. Moreover, under *Levine*, the burden is on the drug manufacturer to show that the FDA would have prevented compliance with the state-law duty to warn by not permitting a proposed labeling change that would have provided the injured consumer with an adequate warning.

2. The generic manufacturers also have not established that implied frustration preemption bars these state tort suits. Such preemption can be found only if state law frustrates achievement of the purpose of the federal statute. The purpose of the 1984 Hatch-Waxman Amendments to the FDCA is to increase the availability of low-cost generic drugs, but in a safe manner. Achievement of this purpose is not frustrated by a state-law tort duty that requires generic manufacturers to warn consumers of known safety concerns.

a. As shown by *Levine*, the presumption against preemption operates with particular importance and weight in these cases. The Court starts with a strong assumption that Congress did not intend to bar long-standing state-law causes of action which protect consumer health and safety.

b. The absence of an express preemption provision in the FDCA is powerful evidence that Congress did not intend to prohibit all state tort suits of this kind. As evidenced by the FDCA's express preemption

clause for medical devices, Congress can be expected to speak explicitly if it intends to bar tort claims for inadequately labeled generic drugs.

c. The generic manufacturers' overstated assertions of frustration-of-purpose fall well short of showing a clear congressional intent to preempt all state tort claims of the sort asserted here. Avoiding liability in these cases did not require the generic manufacturers to conduct expensive studies and raise their drug prices accordingly. The allegations are simply that published medical literature and existing adverse event reports received by the manufacturers revealed the clear need for a new label warning.

d. Important public policy considerations also weigh against implying frustration preemption in these cases. In particular, implied preemption would deny injured consumers of generic drugs a remedy, one they would have if their prescription had instead been filled with the brand-name drug. It also would result in generic manufacturers having no financial incentive to ensure the adequacy of warnings, even if they know the labeling is inadequate and the brand-name manufacturer has abandoned the market entirely to generics. These and other important public policy considerations further underscore that the Court should not ascribe to Congress an unannounced decision to allow generic manufacturers to sell inadequately labeled drugs with impunity.

ARGUMENT

The Court's preemption analysis is "guided by two cornerstones" – congressional intent and the presumption against preemption. *Wyeth v. Levine*, 129 S. Ct. 1187, 1194 (2009). "[T]he purpose of Congress is the ultimate touchstone in every pre-emption case." *Id.* (quoting *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996)). Congress's purpose in enacting the FDCA was "to bolster consumer protection against harmful products," *Levine*, 129 S. Ct. at 1199, with a recognition that "state-law remedies further consumer protection by motivating manufacturers to produce safe and effective drugs and to give adequate warnings." *Id.* at 1200.

The FDCA does not contain an express preemption provision for prescription drugs. *Levine*, 129 S. Ct. at 1200. This leaves the generic drug manufacturers to rely on implied conflict preemption, which comes in two forms: impossibility preemption and frustration (or obstacle) preemption. *See, e.g., Pacific Gas & Elec. Co. v. State Energy Res. Conservation & Dev. Comm'n*, 461 U.S. 190, 203-04 (1983).

The presumption against preemption applies fully to assertions of implied preemption. *Levine*, 129 S. Ct. at 1195 n.3. Moreover, the presumption is especially strong with respect to preserving state law that, as here, is related to health and safety. *See Hillsborough County v. Automated Med. Labs., Inc.*, 471 U.S. 707, 715-20 (1985); *see also Lohr*, 518 U.S. at 475 ("Throughout our history the several States have

exercised their police powers to protect the health and safety of their citizens."); *Altria Group, Inc. v. Good*, 129 S. Ct. 538, 543 (2008) (reiterating that the presumption "applies with particular force when Congress has legislated in a field traditionally occupied by the States").

In applying the presumption against preemption, a congressional intent to displace state law will not be found unless it is "clear and manifest." *Levine*, 129 S. Ct. at 1195 (quoting *Lohr*, 518 U.S. at 485 and *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218, 230 (1947)). Overcoming the presumption imposes a "considerable burden" on the advocate of preemption. *De Buono v. NYSA-ILA Med. & Clinical Servs. Fund*, 520 U.S. 806, 814 (1997).

Under these principles, implied preemption of state law is rarely found, particularly in the area of prescription drugs. *Levine*, 129 S. Ct. at 1194-1204. Like their brand-name counterparts, generic manufacturers were not given congressional *carte blanche* to violate state law by selling prescription drugs without adequate warnings.

I. FEDERAL LAW DOES NOT MAKE IT IMPOSSIBLE FOR GENERIC DRUG MANUFACTURERS TO COMPLY WITH THEIR STATE-LAW DUTY TO ADEQUATELY WARN CONSUMERS OF DANGEROUS SIDE EFFECTS.

Impossibility preemption applies only when it is a "physical impossibility" to comply with both the state and federal law. *Florida Lime & Avocado Growers, Inc. v. Paul*, 373 U.S. 132, 142-43 (1963). This occurs when federal law forbids what state law requires or vice versa. *Barnett Bank v. Nelson*, 517 U.S. 25, 31 (1996).

The state tort failure-to-warn suits at issue here are of the same type that *Levine* permits against brand-name manufacturers. 129 S. Ct. at 1190-93. State tort law has long provided that manufacturers of prescription drugs are liable for harm to consumers caused by inadequate warnings of risks of harm. *Restatement (Third) of Torts: Prods. Liab.* § 6 (1998).

"Impossibility pre-emption is a demanding defense" in such cases. *Levine*, 129 S. Ct. at 1199. The generic manufacturers cannot satisfy this heavy burden. As in *Levine*, the manufacturers are not prevented from complying with their state-law duty to warn by the FDCA and its implementing regulations.

A. Federal Law Does Not Forbid Generic Manufacturers From Adding A New Label Warning.

All prescription drug manufacturers, both brand-name and generic, are responsible for ensuring that the labels of their drugs contain adequate warnings. "[T]hrough many amendments to the FDCA and to FDA regulations, it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times." *Levine*, 129 S. Ct. at 1197-98.

Under the FDCA, a drug "shall be deemed to be misbranded" unless "its labeling bears . . . such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users." 21 U.S.C. § 352(f)(2). To implement this prohibition against misbranded drugs, the FDA requires that prescription drug "labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug." 21 C.F.R. § 201.80(e); *see also* 21 C.F.R. § 201.57(c)(6). The Hatch-Waxman Amendments, 21 U.S.C. § 355(j), do not exempt generic drugs from these fundamental consumer-protection requirements.

The parties disagree regarding how the FDCA and its implementing regulations allow generic

manufacturers to warn consumers of potential side effects that surface after FDA approval of the drug and its original labeling. In any event, it is agreed that, at a minimum, a generic manufacturer can inform the FDA when the need for a change in label warnings for its drug becomes apparent. In fact, the federal government states that the FDCA and FDA regulations obligate generic manufacturers to do so. Brief for the United States as Amicus Curiae (Nov. 2010) ("U.S. Cert. Br.") at 11, 15 (stating that "a generic pharmaceutical manufacturer, like a brand-name manufacturer, can (and indeed, must) inform FDA of new information about risks that may require a change in the labeling of its drug" and that the petitioner generic manufacturers "were obligated to provide FDA with information about labeling concerns").

The undisputed manner in which generic manufacturers can notify the FDA of a labeling inadequacy and propose a new label warning is set forth in the FDA's notice promulgating final rules to implement the 1984 Hatch-Waxman Amendments. The notice instructs generic manufacturers as follows:

> If an ANDA applicant [i.e., a generic drug manufacturer] believes new safety information should be added to a product's labeling, it should contact FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised. After approval of an ANDA [a generic drug], if an ANDA holder believes that new safety

> information should be added, it should provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and listed [brand-name] drugs should be revised.

57 Fed. Reg. 17,961. For "serious safety concerns" (such as the risk of developing tardive dyskinesia from long-term use of metoclopramide), this procedure results in an FDA "substantive evaluation like that for a [proposed label change using the prior approval supplement (PAS) process] under 21 C.F.R. 314.70." U.S. Cert. Br. 16-17. The FDA gives a high priority to the review of labeling changes that generic manufacturers propose for serious safety concerns. *Id.* at 16. If the FDA approves the proposed change, it requires all manufacturers of the brand-name and generic forms of the drug to revise their label warnings in the same way. *Id.* at 15-16.[1]

It is clear, then, that the FDCA and its implementing regulations allow, if not require, a generic manufacturer to notify the FDA and propose a new label warning when the manufacturer becomes aware of dangerous side effects from the use of its drug. Thus, because generic manufacturers are certainly

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[1] The standard used to evaluate such a proposed label change is essentially the same as in the "changes being effected" (CBE) procedure, under which a manufacturer can put a proposed label change in place while FDA approval is pending. Thus, the only practical difference in the two procedures is how quickly the manufacturer can put the change into effect, i.e., either pending or after FDA approval. U.S. Cert. Br. 22-23 n.10.

not prohibited from requesting and obtaining FDA approval to add such a new label warning, federal law does not make it impossible for them to comply with their state-law duty to warn.

B. The Generic Manufacturers Have The Burden To Show That The FDA Would Have Rejected A Proposed Labeling Change.

The generic manufacturers incorrectly argue that any state tort failure-to-warn claim is barred by impossibility preemption because the FDA might have denied a requested labeling change and thereby prevented them from adequately warning consumers. This argument is contrary to *Levine*, which likewise involved a drug manufacturer's failure to seek FDA approval to change an inadequate label. *See Levine*, 129 S. Ct. at 1199 (concluding that, based on the record made at trial, "[w]e . . . cannot credit [the drug manufacturer's] contention that the FDA would have prevented it from adding a stronger warning" to the drug's label). As the proponents of preemption, the generic manufacturers have the burden to show impossibility of compliance with both state and federal law by establishing that the FDA would have rejected a proposed labeling change. *Id.* at 1196-99. "[A]bsent clear evidence that the FDA would not have approved a change to [the drug's] label, [the Court] will not conclude that it was impossible for [the drug

manufacturer] to comply with both federal and state requirements." *Id.* at 1198.[8]

Even if Respondents were assigned the burden of proving that the FDA would have approved a proposed labeling change, it is apparent they could meet that burden given the FDA's subsequent action regarding the label for metoclopramide. In February 2009, the FDA, acting on its own initiative, required manufacturers of metoclopramide to add to the label a warning of the risk of developing tardive dyskinesia from long-term use of the drug. Joint Appendix (JA) at 406, 415, 521, 556. Thus, it is fair to conclude that the FDA would have approved such a label change if it had been proposed earlier by a manufacturer.

Consumers should not, however, be entirely dependent on FDA-initiated action to be warned of dangerous side effects, especially in light of the FDA's limited resources to affirmatively monitor drug safety. *See Levine*, 129 S. Ct. at 1202 & n.11 (recognizing FDA's limited resources). When a generic manufacturer is aware of the need for a change to its label warnings, and yet does nothing to make the change,

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[8] Also without merit is any assertion that impossibility preemption applies on the ground that a generic manufacturer could not have changed the drug's label until the FDA approved the proposed change. The tort claims in the instant cases do not seek to hold the manufacturers liable for such an interim period. *See infra* p. 21.

the manufacturer can certainly be held liable under state tort law for the resulting harm to consumers.

II. THE FDCA DOES NOT IMPLIEDLY PREEMPT ALL STATE TORT FAILURE-TO-WARN CLAIMS AGAINST GENERIC DRUG MANUFACTURERS AS PURPORTEDLY FRUSTRATING THE PURPOSE OF THE 1984 HATCH-WAXMAN AMENDMENTS.

Implied frustration-of-purpose preemption can exist only if the state law "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress" in enacting a federal statute. *Hines v. Davidowitz*, 312 U.S. 52, 67 (1941). Such preemption does not exist here because the requisite clear and manifest congressional intent to implicitly negate state law on that basis cannot be found. The 1984 Hatch-Waxman Amendments to the FDCA did not sacrifice safety in the interest of lower drug costs. Making low-cost generic drugs available in a safe manner is certainly not frustrated by requiring generic manufacturers to adequately warn of dangerous side effects that are readily apparent to them. Especially in light of the public policy consequences, Congress cannot be deemed to have barred injured consumers from holding generic manufacturers accountable for failing to satisfy this basic requirement of state law.

A. There Is A Strong Presumption Against Preemption.

As *Levine* makes clear, the presumption against preemption is especially critical when evaluating an assertion of implied frustration preemption of state tort claims. 129 S. Ct. at 1195 n.3. The Court stated that in such cases "[w]e rely on the presumption because respect for the States as independent sovereigns in our federal system leads us to assume that Congress does not cavalierly pre-empt state-law causes of action." *Id.* (internal quotations omitted). This prevents implied frustration preemption from being misused to displace too much state law.[3]

Moreover, the presumption is enhanced here because the challenged state tort law relates to the health and safety of victims of inadequately labeled

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[3] *See Geier v. American Honda Motor Co.*, 529 U.S. 861, 907-08 (2000) (Stevens, Souter, Thomas, Ginsburg, JJ., dissenting) (observing that "the presumption [against preemption] serves as a limiting principle that prevents federal judges from running amok with our potentially boundless (and perhaps inadequately considered) doctrine of implied conflict pre-emption based on frustration of purposes"); *Bates v. Dow Agrosciences LLC*, 544 U.S. 431, 459 (2005) (Thomas, J., joined by Scalia, J., concurring in the judgment in part and dissenting in part) (approving "th[e] Court's increasing reluctance to expand federal statutes beyond their terms through doctrines of implied pre-emption"); *Gade v. National Solid Wastes Mgmt Ass'n*, 505 U.S. 88, 111 (1992) (Kennedy, J., concurring in part, concurring in judgment) ("A free wheeling judicial inquiry into whether a state statute is in tension with federal objectives would undercut the principle that it is Congress rather than the courts that pre-empts state law.").

prescription drugs. *See supra* pp. 5-6; *Levine*, 129 S. Ct. at 1195 n.3 (recognizing that enforcement of the state tort law requirement to adequately warn of risks from using prescription drugs is "state regulation of health and safety"); *see also Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 348 (2001) (acknowledging "the historic primacy of state regulation of matters of health and safety" as distinguished from claims of fraud on a federal agency) (quoting *Lohr*, 518 U.S. at 485).

The strong presumption against preemption precludes dismissal of these suits unless the generic manufacturers show a "clear and manifest" congressional intent, *Levine*, 129 S. Ct. at 1195, to shield them from all state tort claims that are based on failure to adequately warn of dangerous side effects.

B. The Absence Of An Express Preemption Clause Is Compelling Evidence That Congress Did Not Intend To Bar All State Tort Claims.

In its unanimous opinion in *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, the Court stated: "The case for federal pre-emption is particularly weak where Congress has indicated its awareness of the operation of state law in a field of federal interest, and has nonetheless decided to stand by both concepts and to tolerate whatever tension there is between them." 489 U.S. 141, 166-67 (1989) (internal quotation omitted). Such is the case here.

When it enacted the FDCA in 1938, Congress did not include a provision preempting any type of state tort suits, despite "its certain awareness of the prevalence of state tort litigation." *Levine*, 129 S. Ct. at 1199-2000. Congress did add an express preemption clause to the FDCA in 1976, but only for medical devices. 21 U.S.C. § 360k(a); *see also Riegel v. Medtronic, Inc.*, 552 U.S. 312, 327 (2008) (recognizing that the FDCA's express preemption clause was written specifically to apply only to medical devices, and not to include prescription drugs). Congress did not include a preemption provision in the Hatch-Waxman Amendments enacted eight years later in 1984. Nor has Congress subsequently enacted any preemption provision for prescription drugs, despite continued state tort suits against manufacturers of both brand-name and generic drugs. *See, e.g., Foster v. American Home Prods. Corp.*, 29 F.3d 165, 166-67 (4th Cir. 1994).

From this history, the Court concluded in *Levine*: "If Congress thought state-law suits posed an obstacle to its objectives, it surely would have enacted an express pre-emption provision at some point" such that "[i]ts silence on the issue . . . is powerful evidence that Congress did not intend FDA oversight to be the exclusive means of ensuring drug safety." 129 S. Ct. at 1200. Consistent with Congress's longstanding decision not to enact a provision preempting state tort suits based on inadequate warning of drug risks, the FDA has "traditionally regarded state law as a complementary form of drug regulation." *Id.* at 1202;

see also Cuomo v. Clearing House Ass'n, LLC, 129 S. Ct. 2710, 2718 (2009) (citing *Levine* to refer to prescription drug regulation as one of "many . . . mixed state/federal regimes in which the Federal Government exercises general oversight while leaving state substantive law in place").

The generic manufacturers minimize the importance of Congress's decision not to enact an express preemption provision for prescription drugs, just as they disregard the presumption against preemption. Under the Court's jurisprudence, however, these two factors act together to set a high bar for establishing implied preemption through an asserted frustration-of-purpose.

C. The 1984 Hatch-Waxman Amendments Do Not Abandon The FDCA's Overarching Purpose Of Protecting Consumers From Harm.

"Congress enacted the FDCA to bolster consumer protection against harmful products." *Levine*, 129 S. Ct. at 1199. Because the 1984 Hatch-Waxman Amendments are part of the FDCA, they must be understood with this broader purpose in mind. *See, e.g., Pilot Life Ins. Co. v. Dedeaux*, 481 U.S. 41, 51 (1987) ("On numerous occasions we have noted that '[i]n expounding a statute, we must not be guided by a single sentence or member of a sentence, but look to the provisions of the whole law and to its object and

policy.'") (quoting *Kelly v. Robinson*, 479 U.S. 36, 43 (1986) and other cases).

In their single-minded focus on the Hatch-Waxman Amendments' goal of making low-cost generic drugs available, the generic manufacturers give short shrift to Congress's ultimate purpose of protecting consumers. Such isolation of the Hatch-Waxman Amendments from the entirety of the FDCA violates the basic principle that statutes are to be read as a whole.

Reading the Hatch-Waxman Amendments in concert with the rest of the FDCA, their objective is not just to increase the availability of low-cost generic drugs, but to do so in a manner that protects consumer safety. Streamlining the process for initially bringing generic drugs to market does not mean they are to be sold with no regard for whether consumers are properly warned of serious risks.[4]

This view of the goals of the Hatch-Waxman Amendments is supported by the longstanding recognition that "state law offers an additional, and important, layer of consumer protection that complements FDA regulation." *Levine*, 129 S. Ct. at 1202-03.

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[4] As the Generic Pharmaceutical Association recognizes: "Consumers should be well informed and confident when taking generic drugs." GPhA website, http://www.gphaonline.org/issues/state-consumer-education-efforts (as visited Feb. 11, 2011).

When the Hatch-Waxman Amendments were enacted, state tort suits regarding inadequate warnings had for decades been working in tandem with FDA regulation of drug labeling to protect consumers. These types of state tort "actions, in particular, lend force to the FDCA's premise that manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times." *Id.* As noted above, Congress chose not to put an express preemption clause in the Hatch-Waxman Amendments. This left in place the understanding that consumer protection, as aided by state tort suits, remains the FDCA's guiding purpose for prescription drugs in both their brand-name and generic forms.

D. Requiring Generic Manufacturers To Warn Consumers Of Known Risks Does Not Frustrate Hatch-Waxman's Purpose Of Making Generic Drugs Available At A Low Cost, But In A Safe Manner.

Not only do the generic manufacturers incorrectly focus on just one objective of the Hatch-Waxman Amendments – lowering costs – they attempt to show frustration of that isolated objective by overstating what is required of them to avoid liability in these cases. None of the posited obstacles to the goal of keeping generic drugs affordable is persuasive where, as here, generic manufacturers are alleged to have been aware of the inadequacy of the label warnings for their drug but nevertheless took no action to add a new warning.

First, the generic manufacturers were not required to conduct costly clinical trials in order to notify the FDA of the need to change the label warnings for metoclopramide. Respondents allege that the risk of tardive dyskenisa from long-term use of metoclopramide, for which the label did not carry an adequate warning, was or should have been apparent to the generic manufacturers from published medical literature on the drug and adverse event reports they were receiving. JA 402, 417 (*Mensing*); 522, 559-60 (*Demahy*). Nor do FDA regulations require generic manufacturers to conduct new clinical trials in order to propose a labeling change. The FDA requires only "reasonable evidence" for a change in a label warning. 21 C.F.R. §§ 201.80(e), 201.57(c)(6); *see also* 21 C.F.R. § 314.81(b)(2)(i) (requiring a generic manufacturer to annually report to the FDA information "that might affect the safety, effectiveness, or labeling of [its] drug product"); 21 C.F.R. § 314.98(a) (requiring a generic manufacturer to report adverse drug events to the FDA); *Levine*, 129 S. Ct. at 1197 (recognizing that adverse event reports alone can provide a sufficient basis for a manufacturer to propose a new label warning).

Second, the generic manufacturers also miss the mark in suggesting that they would have to inundate the FDA with unneeded and unexamined information to avoid state tort liability. Again, in cases such as these, liability arises from failure to warn of a dangerous side effect that is apparent from published

literature regarding the drug and adverse event reports received by the generic manufacturer itself.[5]

Third, potential liability for failure to warn in such cases is not likely to cause generic manufacturers to pull products off the market. Such action would be an option only if a manufacturer wrongly believed that it could not even propose a new label warning. *See* JA 416 (*Mensing*) (observing that if the generic manufacturers "realized their label was insufficient but did not believe they could even propose a label change, they could have simply stopped selling the product"). In addition, the claims in the instant cases do not seek to hold a generic manufacturer liable for its drug being inadequately labeled during the period the FDA is deciding whether to approve a timely and appropriate label change proposed by the manufacturer. *See supra* p. 12 n.2; *see also Perry v. Novartis Pharma. Corp.*, 456 F. Supp.2d 678, 687 n.12 (E.D. Pa. 2006) (recognizing that "a manufacturer who has sought FDA approval for an additional warning [should not] be held liable for a failure to warn during the pendency of that agency review"); *Levine*, 129 S. Ct. at 1204 ("Although we recognize that some state-law claims might well frustrate the

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[5] Nor do state tort suits of this kind obstruct a purpose of federal drug regulation by enmeshing the FDA in litigation, any more than did the suit permitted in *Levine*, where the FDA's records were examined in detail to determine if the FDA would have rejected a proposed change in the drug's labeling. *See Levine*, 129 S. Ct. at 1192-93, 1197-99, 1222-26.

achievement of congressional objectives, this is not such a case.").

Furthermore, the continuous exposure of generic manufacturers to state tort suits since enactment of the Hatch-Waxman Amendments in 1984 has not previously caused them to leave the prescription drug market. *See, e.g.*, *Foster*, 29 F.3d at 166-67. On the contrary, the Generic Pharmaceutical Association reports that the sales and market share of generic manufacturers continue to grow. *See* http://www.gphaonline.org/about-gpha/about-generics/facts (as visited Feb. 11, 2011).

E. Public Policy Considerations Also Support The Conclusion That Congress Did Not Intend To Bar All Such State Tort Claims Against Generic Drug Manufacturers.

In light of the foregoing, congressional intent to bar all tort suits of this kind could be found only if public policy reasonably permitted no other conclusion. To the contrary, it is clear that public policy considerations support this role for state law in the regulation of generic drugs. The adverse public policy consequences of preemption are magnified by the fact that 70% of prescriptions in the United States are now filled with generic drugs, a share that amounts to nearly 2.6 billion prescriptions every year. *See* http://www.gphaonline.org/about-gpha/about-generics/facts (as visited Feb. 11, 2011).

1. Injured consumers should have a remedy.

The FDCA does not provide a remedy for injured consumers because Congress determined that "state rights of action provided appropriate relief for injured consumers." *Levine*, 129 S. Ct. at 1199. Thus, implied frustration preemption would leave consumers who are injured by an inadequately labeled generic drug with no remedy, even in cases where the generic manufacturer takes no action in the face of known safety concerns.

Congress should not be deemed to have implicitly granted generic manufacturers such immunity from state law for selling drugs without adequate warnings. *See Bates,* 544 U.S. at 449 ("If Congress had intended to deprive injured parties of a long available form of compensation, it surely would have expressed that intent more clearly."); *Lohr*, 518 U.S. at 487 ("It is, to say the least, 'difficult to believe that Congress would, without comment, remove all means of judicial recourse for those injured by illegal conduct.'") (quoting *Silkwood v. Kerr-McGee Corp.*, 464 U.S. 238, 251 (1984)).[6]

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[6] Moreover, in all but a few states, consumers injured by an inadequately labeled generic drug cannot seek relief against the brand-name manufacturer. As the Eighth Circuit noted, "the overwhelming majority" of courts have concluded that state tort law does not allow consumers of the generic version of a drug to hold the brand-name manufacturer responsible for the inadequacy of label warnings. JA 418-19 (*Mensing*) ("Traditional

(Continued on following page)

2. Similarly-situated consumers should be treated the same.

Implying preemption here would also produce arbitrary and unfair results. Consumers whose prescriptions are filled with the brand-name version of a drug (e.g., Reglan) have a state tort remedy for inadequate label warnings, as held in *Levine*, but consumers whose pharmacists filled their prescriptions with the generic version (e.g., metoclopramide) would be denied a remedy, despite being in precisely the same situation. *See, e.g., McNeil v. Wyeth*, 462 F.3d 364 (5th Cir. 2006) (holding that evidence supporting consumer's inadequate-warning claim against brand-name manufacturer of Reglan precluded summary judgment for manufacturer).

This incongruity is made even worse by the fact that "brand name manufacturers may elect to manufacture and distribute a generic version of their own brand name drug – as Wyeth has done with Reglan – once the brand name drug loses patent protection." *Kellogg v. Wyeth*, 612 F. Supp.2d 437, 441 (D. Vt. 2009). Thus, due to implied preemption, injured consumers using the same drug manufactured by the same company would be treated differently under the law based solely on fortuity.

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products liability requires a plaintiff to show that she actually consumed the defendant's product.").

3. Generic manufacturers should have incentives to warn consumers.

"The FDA has limited resources to monitor the 11,000 drugs on the market" and lacks the capacity to effectively identify all the warnings that should be added based on the emergence of new risks. *Levine*, 129 S. Ct. at 1202 & n.11. State tort suits help fill this breach because they "provide incentives for drug manufacturers to disclose safety risks promptly." *Id.* at 1202.

Implied preemption would remove these tort-law incentives for generic manufacturers, to the detriment of consumer protection and public health. Generic manufacturers would have little inducement to ensure the adequacy of warnings, even when they have specific knowledge of undisclosed health risks. There would be no financial motive for any generic manufacturer to ever propose a labeling change to the FDA, no matter how obvious the inadequacy of a warning might be to it as the maker of the drug.

Moreover, once the brand-name manufacturer stops marketing the drug, it no longer has any tort-law incentives to ensure the adequacy of warnings for newly emerging risks. Thus, if generic manufacturers were immune from suit, there would be no manufacturer left with these strong incentives to ensure the adequacy of label warnings when a drug is being sold in only its generic form. This would undermine the "central premise" of federal drug regulation that manufacturers are responsible for maintaining

adequate drug labeling "at all times." *Levine*, 129 S. Ct. at 1197-98.

4. Costs should not be shifted to taxpayer funded health-care programs.

In addition to denying consumers the protection of state law, implied preemption would put added pressure on state (and federal) budgets. Not only would a significant incentive for ensuring the safe use of prescription drugs be eliminated, but injuries to consumers would go uncompensated by the wrongdoer. Much of the resulting increase in health-care costs would be borne by state-funded programs.

In particular, the Medicaid program, which provides medical assistance for persons who cannot afford to pay their own medical costs, is funded in significant part by the states. 42 U.S.C. §§ 1396a(a)(2), 1396d(b); *see also Arkansas Dep't of Health & Hum. Servs. v. Ahlborn*, 547 U.S. 268, 275 (2006) (explaining that Medicaid is jointly funded by the state and federal governments). Under Medicaid's third-party liability provisions, states can recoup Medicaid payments from the medical-costs portion of tort judgments and settlements. *Ahlborn*, 547 U.S. at 280-92. Implied preemption would prevent the recoupment of such payments caused by a generic manufacturer's tortious failure to warn.

5. Generic substitution laws should not be undermined.

Most states have laws that encourage pharmacies to substitute generics for brand-name drugs. *See, e.g.*, Minn. Stat. § 151.21 (2010); *see also Inwood Labs., Inc. v. Ives Labs., Inc.*, 456 U.S. 844, 847 n.4 (1982) ("Since the early 1970's, most States have enacted laws allowing pharmacists to substitute generic drugs for brand name drugs under certain conditions."); *FTC v. Warner Chilcott Holdings Co. III, Ltd.*, No. 05-2179, 2007 WL 158746, at *1 (D.D.C. Jan. 22, 2007) ("According to the FTC, almost all states and the District of Columbia encourage generic competition through laws and policies that facilitate pharmacies' substitution of lower-priced [bioequivalent] generic drugs for higher-priced branded drugs.").

The consequences of implied preemption are inconsistent with the favored status that these state laws give to generic drugs. The purpose of these longstanding provisions is to encourage the safe use of lower-priced equivalent drugs – not the use of drugs for which there is no remedy if consumers are injured due to inadequate warnings. The public interest is not served by allowing generic manufacturers to reap the financial benefits of state drug-substitution laws while exempting them from compliance with state tort law that protects consumers.

CONCLUSION

The judgments of the Eighth Circuit Court of Appeals and the Fifth Circuit Court of Appeals should be affirmed.

Respectfully submitted,

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AMICUS CURIAE BRIEF

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In the Supreme Court of the United States

PLIVA, INC., ET AL., PETITIONERS

v.

GLADYS MENSING, RESPONDENT

ACTAVIS ELIZABETH, LLC, PETITIONER

v.

GLADYS MENSING, RESPONDENT

ACTAVIS INC., PETITIONER

v.

JULIE DEMAHY, RESPONDENT

ON WRITS OF CERTIORARI TO THE UNITED STATES COURTS OF APPEALS FOR THE EIGHTH AND FIFTH CIRCUITS

BRIEF FOR MORTON GROVE PHARMACEUTICALS, INC. AND IMPAX LABORATORIES, INC. AS *AMICI CURIAE* IN SUPPORT OF PETITIONERS

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QUESTION PRESENTED

The Drug Price Competition and Patent Term Restoration Act (the "Hatch-Waxman Act") allows for the approval of low-cost generic drug products through an abbreviated process that hinges on the requirement that generic drug products—and their warnings—must in all material respects be "the same as" their FDA-approved brand-name equivalents.

Does the Hatch-Waxman Act preempt state-law failure-to-warn claims against the manufacturer of a generic drug whose warnings were, as the Hatch-Waxman Act and the FDA's implementing regulations expressly require, "the same as" those the FDA approved for the product's brand-name equivalent?

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INTRODUCTION AND INTERESTS OF *AMICI CURIAE*

There are two types of duties that state failure-to-warn law might attempt to impose on a generic drug manufacturer: One is to change its label; the other is to provide additional information to the FDA. Petitioners and the Government explain why the first duty is preempted—that is, why any claim that a generic manufacturer failed to change its label cannot be squared with federal law. We agree with their arguments.

We file this brief, however, to explain why federal law preempts not only claims directly seeking a change in generic labeling, but also claims premised on a generic manufacturer's alleged failure to provide sufficient information to the FDA, or to request the FDA's permission to change its label. As this Court recognized in *Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341 (2001), "the relationship between a federal agency and the entity it regulates is inherently federal in character"; it "originates from, is governed by, and terminates according to federal law." *Id.* at 347. Thus, enforcement of the FDCA is "exclusively" the FDA's prerogative; and the "delicate balance" that Congress struck between keeping unsafe products off the market and making efficacious products available may not be "skewed" by allowing "un-

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* The parties have consented to the filing of this brief, and their letters of consent are on file with the Clerk. In accordance with Rule 37.6, *amici* state that no counsel for any party has authored this brief in whole or in part, and no person or entity, other than the *amici*, has contributed monetarily to the preparation or submission of this brief.

predictable civil liability" under state tort law to piggyback on the federal regime. *Id.* at 348, 350, 352.

Amici are manufacturers of generic drugs, and defendants in a slew of similar cases. Indeed, Morton Grove Pharmaceuticals has been a named defendant in more than 500 metoclopramide cases. *Amici*'s concern is that, unless these state failure-to-warn claims are held categorically preempted, this type of liability will put generic manufacturers in an impossible situation, raise the price of generic drugs, and impose costs on the FDA—all in violation of federal law.

These suits are particularly hard on smaller generic companies like *amicus* Morton Grove, which can stay in business only because of the lower costs of generic drug development. "While estimates of the cost to bring a new branded drug to market are in excess of a billion dollars, the research and development costs for a new generic drug are only 1 to 2 million dollars."[1] Moreover, "[t]he relatively low costs to entry for generic drugs lead to increased competition, which drive prices for generic drugs down dramatically." *Id.* at 5. Indeed, "growth in the use of generic drugs has generated substantial savings for American consumers"—savings estimated to be $139.6 billion *in 2009 alone*. *Id.* at 2, 6. But if generics must undertake their own research to determine whether to propose label changes to the FDA, these savings will be greatly reduced if not eliminated. Indeed, claims like those sanctioned by the courts below

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[1] ASPE Issue Brief: Office of the Assistant Secretary for Planning & Evaluation, Office of Science and Data Policy–U.S. Department of Health and Human Services, *Expanding the Use of Generic Drugs* 4-5 (Dec. 2010), available at http://aspe.hhs.gov/sp/reports/2010/GenericDrugs/ib.shtml.

threaten to put smaller generics out of business—a problem with which those courts were none too concerned. JA416 (*Mensing*) (suggesting that generic manufacturers "could * * * simply stop[] selling the[ir] product[s]").

At a minimum, the rulings below threaten to work fundamental changes in the way generics do business —multiplying their costs, to the ultimate detriment of consumers and the nation's health care system. That result would be squarely at odds with the Hatch-Waxman Act, which gave birth to the modern generic pharmaceutical industry and ushered in an era of low-cost drugs. That Act is "the supreme law of the land"; "anything in the constitution or laws of any state to the contrary" must yield. U.S. Const. Art. IV, Cl. 2. The rulings below must therefore be reversed.

STATEMENT OF THE CASE

A. Approval of ANDA and NDA products

For drugs sold in the United States, there are two tracks to FDA approval.

1. First, for new drugs—typically sold, following approval, under a name brand—a manufacturer must submit a new drug application (NDA) establishing that the drug is safe and effective when used as labeled. 21 U.S.C. §355(b); 21 C.F.R. §314.50. To that end, an NDA must include data demonstrating that the drug is safe and effective; analysis of the drug's composition; explanation of the methods and controls used for manufacturing, processing, and packing the drug; and proposed labels. 21 U.S.C. §355(b)(1)(A)-(F); 21 C.F.R. §314.50(d)-(f). Further, before filing an NDA, the manufacturer must obtain authorization to conduct clinical trials to establish the drug's safety

and efficacy to treat a specific condition. 21 U.S.C. §355(i); 21 C.F.R. §§ 312.2, 312.20.

The NDA process is intensive. A typical NDA spans thousands of pages and is grounded in clinical trials conducted, on average, over seven years. GAO, *New Drug Development, Report to Congressional Committees*, 26 Biotech. L. Rep. 82, 94 (2007). On average, the FDA spends some 442 days evaluating NDA submissions. *Id.* at 86.

2. Whereas NDA approval turns on establishing that a drug is safe and effective, the second track to FDA approval—an abbreviated new drug application (ANDA)—turns on establishing that the drug is "the same as" an FDA-approved NDA drug. 21 U.S.C. §355(j); 57 Fed. Reg. 17950, 17953 (April 28, 1992). These "generic" drugs must be identical to an approved NDA drug with respect to active ingredient, route of administration, dosage form, strength, and conditions of use. 21 U.S.C. §355(j)(2)(A)(i); 21 C.F.R. §314.92(a)(1).[2] Moreover, an ANDA must establish that the generic drug is therapeutically equivalent or "bioequivalent" to, and will be given the same labeling as, the name-brand drug. 21 U.S.C. §355(j)(2)(A); 21 C.F.R. §314.94(a). Use of the same label is critical because "[d]rug labeling serves as the standard under which FDA determines whether a product is safe and effective." 50 Fed. Reg. 7452, 7470 (Feb. 22, 1985).

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[2] At FDA's discretion, the ANDA process may also be used for a drug with one different active ingredient, or whose route of administration, dosage form, or strength differs from the NDA product. 21 U.S.C. §355(j)(2)(C); 21 C.F.R. §314.93; see generally 57 Fed. Reg. at 17951-17952.

Generic manufacturers need not (and do not) provide clinical evidence of safety or efficacy. The point of Hatch-Waxman, after all, was "to get generic drugs into the hands of patients at reasonable prices—fast." *In re Barr Labs., Inc.*, 930 F.2d 72, 76 (D.C. Cir. 1991).[3] Accordingly, Congress directed the FDA to approve any product that is a true generic—*i.e.*, bioequivalent to the branded drug and sold with identical labeling. The FDA will reject any ANDA drug that flunks these criteria. 21 C.F.R. §314.127.

The requirement that a generic label be "the same as" the brand-name equivalent has only two statutory exceptions: a generic label may reflect a difference in active ingredient, dosage form, strength, or route of administration that has been vetted and approved under 21 U.S.C. §355(j)(2)(C) (see *supra* n.2), and it may reflect the fact that the generic and name-brand products "are produced or distributed by different manufacturers." 21 U.S.C. §355(j)(2)(A)(v). This second exception encompasses "omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under * * * the act." 21 C.F.R.

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[3] See also, *e.g.*, "P.L. 98-417, Drug Price Competition and Patent Term Restoration Act," H.R. Rep. No. 857(I), 98th Cong., 2d Sess. (1984), reprinted in 1984 U.S.C.C.A.N. 2647, Pet. App. 122; New Drug Application: Hearings on H.R. 3605 Before the Subcomm. On Health and the Environment of the House Comm. on Energy and Commerce, 98th Cong., 1st Sess. (1983), Pet. App. 114a; Drug Price Competition and Patent Term Restoration Act of 1984, Committee Notes, 130 Cong. Rec. 24416, H.R. 3605 (Sept. 6, 1984), Pet. App. 136a; Drug Price Competition and Patent Term Restoration Act, Committee Notes, 130 Cong. Rec. 24970, S. 1538 (Sept. 12, 1984).

§314.94(a)(8)(iv). These exceptions are not at issue here.

B. Post-approval label-change and reporting requirements

1. The rules governing modification of generic product labeling are simple. Indeed, there is only one: The generic label must at all times remain "the same as" the FDA-approved label for the name-brand equivalent. If the FDA approves changes to a brand's label, all generics must change their labels too. Otherwise, the generic label may not be modified.

For example, the FDA's "changes being effected" (CBE) rule allows manufacturers to revise name-brand drug labels to "add" or "strengthen" a "contraindication, warning, precaution, or adverse reaction," where warranted by newly discovered information. 21 C.F.R. §314.70(c)(6)(iii)(A). As discussed below (at 15), however, generics may not use the CBE process to make a label change resulting in a label that differs from the brand's.

FDA regulations also provide for a "prior approval supplement" (PAS) process for making "major" label changes. 21 C.F.R. §314.70(b). This process, however, is not available for strengthening warnings—which changes must be made through the CBE process. 21 C.F.R. §314.70(b)(2)(v)(A).

Manufacturers may also provide information regarding their products, including warnings, through "Dear Health Care Professional" (DHCP) letters. Such letters, however, are "labeling" under federal law. 21 U.S.C. §312(m); 21 C.F.R. §202.1(*l*)(2). Accordingly, generic manufacturers may not send DHCP letters unilaterally, because doing so could create the misimpression that there is a difference

between generic and name-brand drugs—which would constitute misbranding. See CVSG Br. 17-18. DHCP letters therefore require FDA approval.

If a generic manufacturer deviates from the FDA-approved labeling for the branded drug—including by failing to modify its label to match changes made to the brand's—the FDA may withdraw approval. 21 C.F.R. §314.150(b)(10); 21 C.F.R. §314.150(b)(3); see also 57 Fed. Reg. at 17961, 17970.

2. All manufacturers, including generics, must report adverse reactions to the FDA. 21 U.S.C. §355(e), (k); 21 C.F.R. §§ 314.80(c), 314.81, 314.98; see also 21 U.S.C. §331(e). The FDA may investigate and punish non-compliance with a wide range of sanctions, including withdrawal of approval (21 U.S.C. §355(e); 21 C.F.R. §§ 314.80(j), 314.81(d), 314.150(b)(1)); injunctions (21 U.S.C. §332(a)); criminal penalties (*id.* §333(a)); civil monetary penalties (*id.* §333(f)(3)(A)); seizure (*id.* §334(a)); and enforcement proceedings (*id.* §337(a)). The FDCA also preserves the FDA's discretion to take less stringent action where appropriate. 21 U.S.C. §§ 336, 375(b).

The FDA "thus has at its disposal a variety of enforcement options." *Buckman*, 531 U.S. at 349 (footnote omitted). It uses this authority "to punish and deter fraud against the Administration, and * * * to achieve a somewhat delicate balance of statutory objectives." *Id.* at 348. In deciding how best to enforce the FDCA, the FDA enjoys unreviewable discretion (*Heckler* v. *Chaney*, 470 U.S. 821, 837-838 (1985)), and "all * * * proceedings for the enforcement, or to restrain violations, of this chapter shall be by and in the name of the United States" (21 U.S.C. §337(a)).

3. The Food And Drug Administration Amendments Act of 2007 (FDAAA), Pub. L. No. 110-85, 121 Stat. 823, gave the FDA additional tools to regulate prescription drugs. Most notably, the FDA may require post-approval studies of drugs; demand labeling changes; require changes in the risk evaluation and mitigation strategy now required for many drugs; and impose substantial civil penalties for non-compliance. 21 U.S.C. §§ 355(o), 355-1(g), 333(f).

Significantly, in 21 U.S.C. §355(o)(4), Congress directed the FDA to provide notice of label changes to the NDA holder. Manufacturers of generic drugs under approved ANDAs are given notification—and the burden of responding to FDA-proposed changes—only when the NDA holder is no longer marketing the product. *Ibid.*

C. Proceedings below

Respondents developed tardive dyskinesia, a neurological disorder, after long-term use of metoclopramide. They were prescribed the name-brand version of that drug, Reglan, and their prescriptions were filled with generic metoclopramide manufactured by Petitioners. At the time, the FDA-approved label for Reglan warned of the risk of developing tardive dyskinesia. As required, Petitioners' labels for generic metoclopramide provided identical warnings.

Respondents nevertheless filed suit, claiming that Petitioners violated state law by failing to label their products with warnings different from those mandated by the FDA. Misinterpreting federal law and giving short shrift to the requirement that generic products at all times be labeled "the same as" their branded equivalents, the Eighth and Fifth Circuits authorized Respondents to assert not only that Peti-

tioners ought to have departed from their FDA-approved label, but also that they ought to have provided additional warnings *to the FDA*. JA409-416 (*Mensing*); JA554-556 (*Demahy*).

Indeed, according to the Eighth Circuit it matters not whether a generic manufacturer may avail itself of the CBE procedure that was so critical to this Court's decision in *Wyeth* v. *Levine*, 129 S. Ct. 1187 (2009), because state law may require the manufacturer to "take steps" to provide a new warning—*i.e.*, to "*propose*[] a label change that the FDA could receive and impose uniformly on all metoclopramide manufacturers." JA409-410 (*Mensing*). The Fifth Circuit similarly concluded that, without regard to the CBE process, state law may require a generic manufacturer to "alert the FDA and provide supporting scientific data; and the FDA then makes the decision whether such a labeling change is supported by science." JA554 (*Demahy*).

SUMMARY OF ARGUMENT

The decisions below rest on two premises: first, that generic manufacturers may unilaterally initiate changes to their product labels via means such as the CBE process, the PAS process, and DHCP letters; and second, that even apart from the availability of these processes, state tort law may regulate generic drug manufacturers' relationship with the FDA, by imposing hefty damage awards on perceived failures to provide the agency with sufficient information. Neither premise, however, can be reconciled with the text, structure, or purpose of the Hatch-Waxman Act—or with this Court's precedents.

I. State law may not hold manufacturers liable for selling generic drugs with labeling that is "the same as" the brand-name equivalent. This is not a generic manufacturer's choice; it is a mandate of federal law. It is thus *impossible* for generic manufacturers to comply with any duty under state tort law requiring a warning different from, or in addition to, what the FDA has approved for the brand-name drug. And the fact that generic manufacturers may not unilaterally alter, add to, or otherwise depart from FDA-approved labels distinguishes these cases from *Wyeth* v. *Levine*, 129 S. Ct. 1187 (2009). This is not even a close question.

II. In addition, however, States may not hold generic manufacturers liable in tort for failing to provide information to the FDA that supposedly *would have* (according to a lay jury) led the agency to order label changes. The courts below approved state tort claims premised on the notion that a manufacturer has a duty to "'provide adequate supporting information to FDA,'" and thus "could * * * at least *propose*[] a label change that the FDA could receive and impose uniformly." JA410 (*Mensing*); JA554-556 (*Demahy*). But such claims cannot be reconciled with *Buckman Co.* v. *Plaintiffs' Legal Committee*, 531 U.S. 341 (2001), which held that the FDA alone is responsible for policing communication between the agency and the manufacturers it regulates. There, as here, lower courts had recognized state tort liability premised "solely [on] the violation of * * * the FDCA disclosure requirements." *Id.* at 352-353. But as the Court recognized, such litigation "would exert an extraneous pull on the scheme established by Congress," and is therefore preempted. *Id.* at 353.

A. As a threshold matter, no presumption against preemption applies to state tort claims that hinge on a generic company's failure to warn the FDA. Such a claim has never been part of traditional state regulation of health and safety; it is a newly devised overlay, premised on and arising solely out of *federal* law. As *Buckman* explained, "the relationship between a federal agency and the entity it regulates is inherently federal in character because the relationship originates from, is governed by, and terminates according to federal law." 531 U.S. at 347. Indeed, even the concurring Justices in *Buckman* would have found preempted state tort law theories that "depend upon speculation as to the FDA's behavior in a counterfactual situation." *Id.* at 354 (Stevens and Thomas, JJ., concurring in judgment).

B. Even apart from application of a presumption against preemption, *Buckman* confirms that state law cannot be allowed to police manufacturers' relationship with the FDA.

The ANDA process, even more so than the §510(k) process at issue in *Buckman*, "sets forth a comprehensive scheme for determining whether an applicant has demonstrated that a product is * * * equivalent to a predicate [drug]." *Id.* at 348. Moreover, enforcing the FDCA is the FDA's "exclusive[]" prerogative, and the agency may prefer a "measured response" to a generic's alleged failure to submit "additional necessary information." *Id.* at 348, 349, 352. That is because the FDA is charged with striking "a somewhat delicate balance" between keeping unsafe products off the market and making efficacious products available to patients. *Id.* at 348. That balance may not be "skewed" by allowing "unpredictable civil liability" under state law to piggyback on the federal regime.

Id. at 348, 350. Such a result would raise the stakes exponentially for generics, working wholesale changes in the way such companies do business and ultimately discouraging development of needed low-cost drugs. See *id.* at 348, 350.

Indeed, unless generic manufacturers do exactly what Hatch-Waxman was designed to prevent—*i.e.*, spend time and money replicating the brand's studies and creating a knowledge base for evaluating new data that might warrant revisiting the scientific and practical trade-offs embodied in the FDA-approved label—they cannot comply with the duties imposed by the decisions below. If the point of Hatch-Waxman was to affirmatively encourage low-cost generic drugs, then surely federal law will not countenance state regulation that multiplies the cost of generic drugs by purporting to oversee the *federal* regulatory scheme. *Buckman*, 531 U.S. at 350.

Finally, such potential state liability gives regulated entities "an incentive to submit a deluge of information that the Administration neither wants nor needs, resulting in additional burdens on the FDA[]." *Buckman*, 531 U.S. at 351. *Amici* have an interest in an FDA that operates quickly and efficiently—goals quite consistent with the best interests of patients, who need safe and effective drugs sooner rather than later. What no one needs is a generic pharmaceutical industry that cannot protect itself from state tort liability unless it inundates the FDA with information, suggestions, cautions, and incessant proposals to reconsider drug labels.

Yet, under the decisions below, if the FDA has not rejected the most risk-averse label clever minds can devise—and every variation short of it—then injured

plaintiffs can ask lay juries whether a manufacturer should have made a particular pitch, and whether, had that pitch been made, the FDA would have acted. The parties will be forced to seek both written discovery regarding the agency's internal decision-making process and testimony concerning how agency personnel would have responded to various hypothetical scenarios. The result will be precisely what the Court warned against in *Buckman*: serious interference with the FDA's resources and enforcement of the FDCA.

For all these reasons, the decisions below should be reversed, and state law failure-to-warn claims against manufacturers of generic drugs held categorically preempted.

ARGUMENT

I. Federal Law Preempts Claims That A Generic Manufacturer Should Have Changed Its Label.

As Petitioners and the Government explain, federal law dictates that generic drug labels be "the same as" the FDA-approved label for the name-brand equivalent—both before and after the ANDA's approval. And since federal law requires generic drug labels to contain a specific set of cautions—and none other—it is *impossible* for generic manufacturers to comply with state law requirements to provide additional warnings. If a warning is not part of the FDA-approved label, generic manufacturers may not give it. For generic drugs, federal labeling requirements "serve as a ceiling as well as a floor." *Wyeth*, 129 S. Ct. at 1204 (Breyer, J., concurring).

A. Generic labeling must be "the same as" the name-brand equivalent.

To prevent consumers from erroneously thinking a name-brand drug is somehow better (or worse) than its generic copies, and to decrease the cost of generic drugs, Congress mandated that generic drugs have "the same" labels as their name-brand equivalents. 21 U.S.C. §355(j)(2)(A)(v). This is a condition of FDA approval, and a manufacturer may no more ignore this requirement post-approval than it could change the drug's active ingredient. Federal law places "a very high priority [on] assuring consistency in labeling * * * to minimize the cause for confusion among health care professionals and consumers as well as to preclude a basis for lack of confidence in the equivalency of generic versus brand name drug products." Division of Generic Drugs, FDA, *Policy & Procedure Guide* 37 (1989).

As discussed above (at 5), there are only two statutory exceptions to this requirement—and neither includes stronger safety warnings. Indeed, in adopting final ANDA regulations in 1992, the FDA rejected proposals that "FDA accept ANDA's with warnings or precautions in addition to those on the reference listed drug's label." 57 Fed. Reg. at 17953; accord *id.* at 17957. As detailed by Petitioners PLIVA, Inc., et al. (at 19-20, 38-40), the FDA has maintained this position for decades. But according to Respondents, generic manufacturers may unilaterally revise their labels via the CBE process, initiate label changes via the PAS process, and provide information to doctors via DHCP letters. Respondents are wrong on every count.

B. Generic manufacturers may not unilaterally change their product labeling.

1. CBE process

The "changes being effected" (CBE) process, 21 C.F.R. §314.70(c), was central to this Court's holding in *Wyeth*. See 129 S. Ct. at 1196, 1199 (impossibility analysis literally starting and ending with the CBE regulation). That process allows brands to alter drug labels to "add or strengthen a contraindication, warning, precaution, or adverse reaction," or to "add or strengthen an instruction about dosage and administration that is intended to increase the [drug's] safe use," where warranted by newly discovered information. *Id.* at 1196 (quoting 21 C.F.R. §314.70(c)(6)(iii)-(A), (C)).

By the Fifth Circuit's reasoning, the FDA's CBE regulation "does not, on its face, distinguish between generic and name brand drug manufacturers," and thus "does not forbid a generic manufacturer from using the CBE process to unilaterally change a label." JA543 (*Demahy*). The Eighth Circuit took a similar view. JA412-413, 414-415 (*Mensing*). But as the Government explains (CVSG Br. 13-14), generics may use this process *only* to make changes already approved for the brand's label. The CBE regulation must be read in conjunction with the substantive standards governing generic labeling—including the rule that ANDAs will not be approved unless the generic's proposed labeling *is* "the same as" the name-brand equivalent, and the rule that approval will be withdrawn unless that labeling *stays* "the same as" the brand's. 21 U.S.C. §355(j)(4)(G); 21 C.F.R. §314.94(a)(8)(iii); 21 C.F.R. §314.150(b)(10).

Given that ANDA approval may be withdrawn if "the labeling for the drug product that is the subject of the abbreviated new drug application is no longer consistent with that for the listed drug" (21 C.F.R. §314.150(b)(10)), it makes no sense to read the "same as" limitation as applying during the approval stage, but not afterwards. Accord Proposed Rule, 73 Fed. Reg. 2848, 2849 n.1 (Jan. 16, 2008). Rather, generic manufacturers are required to conform to the approved labeling for the listed drug *at all times*.

For generic products, therefore, the CBE process provides nothing more than a mechanism to maintain consistency with the brand's labeling *if* that labeling changes. It does not permit complying with rules of state tort law providing that generic drugs ought to carry more fulsome warnings. If the brand's label changes, so too must the generic's; but if the brand's label has not changed, neither may the generic's.

2. PAS process

Nor may generic manufacturers use the PAS process to add or strengthen warnings on their labels.

The text of the FDA's PAS regulations is dispositive: "[C]hanges [requiring pre-approval] include, but are not limited to * * * the following label changes: Changes in labeling, except those described in paragraph[] (c)(6)(iii) * * * of this section." See 21 C.F.R. §314.70(b)(2)(v)(A). That exception is a cross-reference to the CBE provision quoted above, which governs strengthened warnings. And as we have shown, the CBE process is unavailable to generics seeking to implement labels that differ from the brand's.

3. DHCP letters

Finally, Respondents propose that generic manufacturers can provide warnings to doctors and patients, above-and-beyond FDA-approved labeling, by sending "Dear Health Care Professional" (DHCP) letters. Not so.

Because DHCP letters are "labeling" under federal law, they implicate the federal prohibition on misbranding. 21 U.S.C. §312(m); 21 C.F.R. §202.1(*l*)(2). If a generic manufacturer were to unilaterally send a DHCP letter warning of additional risks associated with its product, that would tend to suggest—wrongly—that there is a difference between the generic and brand-name drug. Accordingly, DHCP letters can be sent only with FDA approval or coordination—something the Eighth Circuit recognized. JA413 n.5 (*Mensing*) ("FDA sends [DHCP] letters out on behalf of ANDA holders if it determines that such a letter is * * * necessary"). Generic manufacturers who unilaterally send letters risk having approval for their products revoked. 21 C.F.R. §314.150(b)(3).

* * * * *

The federal regime requires generic drugs to bear "the same" label as their brand-name equivalents—at all times, and in all relevant particulars. In assessing the viability of failure-to-warn suits against manufacturers of name-brand products, the Court in *Wyeth* reasoned that such manufacturers are responsible for the content of their labels, and that federal law provides a mechanism to unilaterally update safety information without prior FDA approval. 129 S. Ct. at 1196-1199. Neither conclusion is true of generic manufacturers. It is therefore impossible for generic

manufacturers to comply with any state tort law requirement to use labeling not mandated by the FDA.

II. Under *Buckman*, Federal Law Preempts Claims That A Generic Manufacturer Should Have Warned Or Provided Additional Information To The FDA.

Although federal law precludes generic manufacturers from unilaterally providing additional, non-FDA-approved warnings to consumers, the courts below concluded that such manufacturers could be held liable for "failing to take steps to change the label"—either by providing the FDA with information as to "additional risks" of their products, or by "*propos[ing]* a label change that the FDA could receive and impose uniformly." See JA534 (Demahy); JA410 (*Mensing*); see also CVSG Br. 11 (suggesting that failure-to-warn claims are not "categorically preempted" because generics must report adverse events to FDA, and may request label changes). But this attempt to carve-out a role for state tort regulation is flatly inconsistent with *Buckman*, and with the text, structure, and purposes of the Hatch-Waxman Act.

A. There is no presumption against preemption of claims that a generic manufacturer should have warned the FDA.

At the outset, we emphasize that these are not cases in which the Court should apply a "presumption against preemption." Cf. *Wyeth*, 129 S. Ct. at 1195 n.3.

1. To begin with, any such presumption is difficult to reconcile with the text and structure of the Constitution itself. The Supremacy Clause provides that all federal law "shall be the supreme law of the land; and the judges in every state shall be bound thereby, any-

thing in the constitution or laws of any state to the contrary notwithstanding." U.S. Const. Art. IV, Cl. 2. This language does not suggest a reticence on the part of the Framers to preempt state law. Rather, they specifically contemplated that rulings of state courts and judges might interfere with the operation of federal law, and made clear that federal law should take precedence "notwithstanding" "*anything* in the constitution or laws of any state *to the contrary*." If anything, this language *undercuts* any presumption against preemption. And as a matter of constitutional structure, limits on federal power should be effectuated by proper interpretation of enumerated federal powers, not by tipping the scales against preemption where Congress validly acted. Cf. *Watters* v. *Wachovia Bank, N.A.*, 550 U.S. 1, 22 (2007).

2. Even if a presumption against preemption were appropriate in other contexts, no such presumption applies in *conflict* preemption cases, much less here. In analyzing whether there is a conflict between federal and state law, it makes no sense—as a matter of logic or common sense—to *presume* that Congress would tolerate such a conflict. Either there is a conflict or there isn't. That, in part, is why "neither an express pre-emption provision nor a saving clause bars the ordinary working of conflict preemption principles." *Buckman*, 531 U.S. at 352 (internal quotation and alteration marks omitted); accord *Geier* v. *Am. Honda Motor Co.*, 529 U.S. 861, 869 (2000).

3. In any case, "policing" manufacturers' "dealings with the FDA"—dealings "prompted by the [FDCA], and the very subject matter of [which] [is] dictated by that statute's provisions"—"is hardly 'a field which the States have traditionally occupied.'" *Buckman*, 531 U.S. at 347-348 (citation omitted). *Wyeth* held

that garden-variety failure-to-warn claims fell within States' historic concern with health and safety regulation, notwithstanding a 100-year history of federal pharmaceutical regulation. 129 S. Ct. at 1195 n.3; but cf. *United States* v. *Locke*, 529 U.S. 89, 108 (2000) (presumption against preemption "is not triggered when the State regulates in an area where there has been a history of significant federal presence"). But claims that generic manufacturers should have provided the FDA with "additional necessary information"—on which the agency allegedly would have acted—do not "implicat[e] 'federalism concerns and the historic primacy of state regulation of matters of health and safety.'" *Buckman*, 531 U.S. at 347-348 (citation omitted); cf. *Boyle* v. *United Techs. Corp.*, 487 U.S. 500, 504-505 (1988) (no presumption against preemption where the interests at stake are "uniquely federal" in nature). Accordingly, "no presumption against pre-emption obtains in this case." *Buckman*, 531 U.S. at 348.

B. Under *Buckman*, States may not police communications between a generic manufacturer and the FDA—and claims based on label change *proposals* require such policing.

Even apart from the absence of any presumption against preemption, several parallels between these cases and *Buckman* confirm that the "taking steps" liability contemplated by the courts below "would exert an extraneous pull on the scheme established by Congress." 531 U.S. at 353. Indeed, the legal context in which these cases arise is strikingly similar.

1. The legal context of these cases is strikingly similar to what the Court evaluated in *Buckman*.

a. The duty at issue here is the same as that alleged in *Buckman*. According to the courts below, even if federal law prohibits generics from unilaterally changing their labels (which it does), such companies may nonetheless be subjected to state tort liability for failing to "take steps" to "alert the FDA" of the need for "a label change that the FDA could * * * impose uniformly." See JA534, 547, 554-556 (*Demahy*); JA410 (*Mensing*). To be sure, the courts did not call this a "fraud" theory. But the central allegation is the same—namely, that the manufacturer breached a duty to disclose "adequate supporting information to FDA" concerning the risks of a product. JA547 (*Demahy*) (citation omitted). And in both cases the lower courts recognized state tort liability premised "solely [on] the violation of * * * the FDCA disclosure requirements." 531 U.S. at 352-353. As *Buckman* confirmed, however, federal law preempts claims that a manufacturer failed to submit "additional necessary information" in its "dealings with the FDA." *Id.* at 347, 348.

b. The FDA approval processes at issue here and in *Buckman* are closely analogous. *Buckman* involved the FDA's abbreviated (§510(k)) process for approving "substantially equivalent" medical devices. These cases involve the FDA's abbreviated (ANDA) process for approving "bioequivalent" generic drugs. In both contexts, approval rests on a showing that the applicant's product is similar or identical to a predicate product—one subjected to more rigorous, "time consuming," and "thorough review." 531 U.S. at 344-345. And in both contexts, the purpose of abbreviated

approval is to get the later product "on the market within a relatively short period of time." *Id.* at 350; see *Barr Labs.*, 930 F.2d at 76 (Hatch-Waxman's fundamental goal is "to get generic drugs into the hands of patients at reasonable prices—fast").

Although the "[Section] 510(k) notification requires little information, rarely elicits a negative response from the FDA, and gets processed very quickly" (*Medtronic, Inc.* v. *Lohr*, 518 U.S. 470, 478-479 (1996) (citation omitted)), this Court found that process to have preemptive effect because, "to achieve its limited purpose, [it] imposes upon applicants a variety of requirements that are designed to enable the FDA to make its statutorily required judgment as to whether the device qualifies" (*Buckman*, 531 U.S. at 348-349). Thus, the fact that an FDA-regulated product relies on safety or efficacy data submitted for a predicate product—and is subject to review "lack[ing] the [earlier] review's rigor"—does *not* make the relationship between the FDA and the manufacturer any less "inherently federal." *Id.* at 347, 348.

Indeed, ANDA products are far more closely tied to NDA drugs than are §510(k) devices to their Class III counterparts. Both the labeling and active ingredient of an ANDA product must be "the same as" the NDA drug's. Manufacturers of §510(k) devices are subject to no comparable requirements. See 21 C.F.R. §807.87(e). Moreover, as discussed below, the FDA enjoys the same enforcement options whether the manufacturer simply failed to provide required information or made affirmative misstatements to the agency. These cases therefore present an even stronger case for preemption than did the facts of *Buckman*.

2. The United States alone has authority to enforce the FDCA, and to decide whether generic labels should be changed.

a. Preemption of failure-to-inform-the-FDA claims is also warranted because, as in *Buckman*, the authority and discretion to take action against a generic manufacturer for noncompliance with federal law rests "exclusively [with] the Federal Government." 531 U.S. at 352. As the Court there explained, "[t]he FDCA leaves no doubt that it is the Federal Government rather than private litigants who are authorized to file suit for noncompliance with the medical device provisions: '[A]ll such proceedings for the enforcement, or to restrain violations, of this chapter shall be by and in the name of the United States.'" *Id.* at 349 n.4 (quoting 21 U.S.C. §337(a)). This is equally true of the reporting requirements at issue here. And the FDA may well prefer a more "measured response" than that of a lay jury hearing one case in isolation. *Id.* at 349.

The Fifth Circuit noted that, because there is no private federal cause-of-action for the failure to warn, consumers of generic drugs have no remedy if state actions are preempted. JA532 (*Demahy*). But this lack of a private damages remedy is by design. As detailed above (at 7-8), the FDA has several means of regulating the conduct of generic manufacturers. The availability of this range of regulatory options "is a critical component of the statutory and regulatory framework under which the FDA pursues difficult (and often competing) objectives." *Buckman*, 531 U.S. at 349. Further, when it determines that the FDCA has been violated, the FDA has "complete dis-

cretion" to pursue the remedy that, in its judgment, best fits the violation. *Chaney*, 470 U.S. at 835.

State tort law policing of communications between regulated entities and the FDA, by contrast, would operate in a vacuum, divorced from any obligation or incentive to balance the goal of full disclosure against other worthy (sometimes competing) policy objectives —such as patients' interest in access to live-saving medicines with significant side effects. Even if state and federal law share the same ultimate goal, "[t]he fact of a common end hardly neutralizes conflicting means." *Crosby* v. *Nat'l Foreign Trade Council*, 530 U.S. 363, 379 (2000). Accordingly, state law is still preempted if it "interferes with the methods by which the federal statute was designed to reach this goal." *Int'l Paper Co.* v. *Ouellette*, 479 U.S. 481, 494 (1987). And since violating one's duties to the FDA "is not a local offense," but an offense against the United States, it is "vital" that enforcement "should be exclusively within the control of the Federal Government." *Pennsylvania* v. *Nelson*, 350 U.S. 497, 505 (1956).

And make no mistake: State tort liability is a form of additional regulation. "The obligation to pay compensation" is "a potent method of governing conduct and controlling policy." *San Diego Bldg. Trades Council* v. *Garmon*, 359 U.S. 236, 247 (1959). Unlike name-brand drugs, generic drugs typically have a thin profit margin—which means these hefty damage awards can be company killers. Just as the Court in *Buckman* recognized that the "fear" of "expos[ing] the manufacturer * * * to unpredictable civil liability" might "discourage [applicants] from seeking §510(k) approval of devices" (531 U.S. at 350), so too may the prospect of liability for an alleged failure to inform

the FDA deter the development of needed low-cost generic medicines.

Allowing failure-to-inform-FDA claims would also allow juries in 50 different States to reach judgments that differ from the FDA's—and from each other's. See *Garner* v. *Teamsters*, 346 U.S. 485, 490-491 (1953) ("A multiplicity of tribunals and a diversity of procedures are quite as apt to produce incompatible or conflicting adjudications as are different rules of substantive law."). Citing this danger, *Buckman* explained that allowing liability under "50 States' tort regimes will dramatically increase the burdens facing potential applicants—burdens not contemplated by Congress." 531 U.S. at 350. The effect was an "inevitabl[e] conflict with the FDA's responsibility to police fraud consistently with the Administration's judgment and objectives." *Ibid.* The same is true of the failure-to-inform-the-FDA claims here.

Indeed, because drugs cross state lines, the rulings below effectively allow the most warning-happy State to set policy for the whole nation, undermining the Act's goal of promoting uniform labels. But "one State's power to impose burdens on the interstate market" is "constrained by the need to respect the interests of other States." *BMW, Inc.* v. *Gore*, 517 U.S. 559, 571 (1996). And where "[t]he subject-matter * * * peculiarly * * * calls for uniform law," States may not "supplement" federal mandates. *Pennsylvania R.R.* v. *Public Serv. Comm'n*, 250 U.S. 566, 569 (1919); see also *Boyle*, 487 U.S. at 507-508.

b. A further problem is that the failure-to-inform-the-FDA claims approved below would allow state law to establish and enforce a labeling standard other than that which was adopted by the FDA and in force

at the relevant time. As even the concurring Justices in *Buckman* recognized, state tort liability should not "depend upon speculation as to the FDA's behavior in a counterfactual situation"; it should be "grounded in the agency's explicit actions." See 531 U.S. at 354 (Stevens, J., concurring). Indeed, States generally may not provide causes of action that fail to give effect to federal administrative decisions that have neither been rescinded by the agency nor set aside by the federal courts. *Arkansas La. Gas Co.* v. *Hall*, 453 U.S. 571 (1981) (*Arkla*); *Chicago & North Western Transp. Co.* v. *Kalo Brick & Tile Co.*, 450 U.S. 311 (1981). The claims here, however, would proceed on the theory that Respondents should receive damages as if marketing a drug approved by the FDA—under a label it mandated—was unlawful.

c. Incredibly, the decisions below would go so far as to put the burden on *defendants* to adduce "clear evidence" that FDA would have *rejected* a labeling proposal. JA409-416 (*Mensing*); JA554-556 (*Demahy*); see also *Gaeta* v. *Perrigo Pharm. Co.*, No. 09-15001, 2011 WL 198420, *10 (9th Cir. Jan. 24, 2011) (reasoning that the FDA's conclusion that there was "no need" to add a hepototoxicity warning "at this time" did *not* amount to "clear evidence that the FDA would have rejected the [plaintiffs'] proposed hepatotoxicity warning *two years later*") (emphasis added).

Misunderstanding *Wyeth*, the courts below reasoned that *Petitioners* bear the burden of proving how FDA would have responded in a counterfactual situation of Respondents' devise. JA415 (*Mensing*); JA555-556 (*Demahy*); see also CVSG Br. 19. As an initial matter, this makes no sense. If a plaintiff's claim is that she was injured by a failure to warn—or, more precisely, that the generic manufacturer

should have provided additional information to the FDA, which would have approved further warnings—then FDA *action* is "an essential link in the chain of causation." See *Buckman*, 531 U.S. at 353 (Stevens, J., concurring). Quite apart from the fatal problems with claims that depend on "speculation as to the FDA's behavior in a counterfactual situation" (*ibid.*), *all* elements of such claims, including causation, are Respondents' burden to prove. Restatement (Second) of Torts §433B(1) (1965).

Furthermore, requiring generic manufacturers to "show the likelihood of FDA *in*action" (JA415 (*Mensing*)) is contrary to the usual rule that those seeking relief from the status quo bear the burden of proof. Cf. *U.S. Bancorp Mortg. Co.* v. *Bonner Mall P'ship*, 513 U.S. 18, 26 (1994); 2 McCormick on Evid. §337 (6th ed. 2009). In *Wyeth*, the Court reasoned that nothing barred name-brand manufacturers from unilaterally strengthening warnings via the CBE process. 129 S. Ct. at 1196-1197. Thus, to establish a conflict between state and federal law, it was necessary to show that the FDA would have acted after the fact to reject a label change made by the brand—a burden that falls on the manufacturer. *Id.* at 1198.

The situation here is fundamentally different. The *starting point* is a conflict between state and federal law: Petitioners must use the FDA-approved label; unlike the defendants in *Wyeth*, they may not unilaterally provide any enhanced warning state law might require; and a conflict thus exists *unless and until the FDA acts*. Here, as in *Wyeth*, one party must show FDA *action* to prevail; that party bears the burden.

Wherever the burden is placed, however, the conflict between state and federal law is not averted by a

jury's conclusion that the FDA would have required a different label had the manufacturer only proposed it. The FDA "alone is empowered" to decide whether generic labels should be altered, and by seeking damages based on assumptions concerning what the FDA "might have done," Respondents seek to "usurp[] a function that Congress has assigned to a federal regulatory body." *Arkla*, 453 U.S. at 581-582.

3. State regulation is an added burden on generic manufacturers and, as such, conflicts with the federal regime.

Allowing state tort claims here would also thwart federal policy favoring inexpensive, widely-available generic drugs, as it would force generic manufacturers to undertake burdens—collecting and analyzing scientific data, and making risk-assessment decisions on pain of substantial liability—that Congress never intended. Cf. *Buckman*, 531 U.S. at 350. Such costs are particularly problematic under Hatch-Waxman, which was enacted to *increase* the availability, and *lower* the cost, of generic drugs.

First, Congress exempted generics from safety and efficacy mandates applicable to brands, replacing those burdens with a lighter burden—to be "the same as" an NDA drug. It would thwart the federal scheme, therefore, to impose on generics the burdens that Congress imposed on brands.

The Government asserts that "petitioners could have asked FDA to coordinate appropriate DHCP letters (or, by extension, to take other action with respect to labeling)." CVSG Br. 11. But Congress made brands—*not* generics—responsible for maintaining labeling. Moreover, the practical reality is that name-brand manufacturers possess the proprietary

information and experience with respect to safety that was necessary to obtain approval in the first place—and can analyze new information against that backdrop.

Generic manufacturers, by contrast, do not have the same proprietary data, experience, or other knowledge, except with respect to bioequivalence. As discussed above, the central and immutable federal obligation imposed on generic manufacturers is to maintain a label "the same as" a branded equivalent. To be sure, federal law does not *forbid* generic manufacturers (or anyone else) from making labeling suggestions to the FDA. But it puts the *obligation* to do so on companies able to make informed suggestions. If generics must attempt to fulfill this role, such companies will be obliged to err on the side of overly stringent warnings—to the detriment of patients who need generic drugs—to avoid being perceived as "soft" on the risks of their products. That would be a perverse system of incentives.

Furthermore, creating the knowledge base necessary to propose label changes has a cost. Indeed, contrary to the courts below (JA416-417 (*Mensing*); JA558-560 (*Demahy*)), generic manufacturers of metoclopramide could not have requested—much less triggered—a label change based simply on articles in the medical literature or their own individual experiences with adverse events. Label changes require fuller scientific substantiation. Such substantiation can be obtained only through analysis of the proprietary clinical studies conducted to obtain approval of the branded drug—information to which generics lack access—or by post-approval studies, which ge-

nerics are not authorized to perform consistent with Hatch-Waxman.[4]

In fact, the decisions below are surprisingly oblivious of the history underlying Hatch-Waxman. Under the old regime, generics had to be priced to reflect the fact that all would-be generic manufacturers had to independently establish safety and efficacy. Allowing the civil liability contemplated by the decisions below would re-impose these costs—which are not small. One calculation put the cost for pre-approval clinical studies for a branded drug at $176.5 million (in 2000 dollars), and the *post-approval* research and development cost for a new drug brought to market at $140 million. Joseph A. DiMasi, et al., *The Price of Innovation: New Estimates of Drug Development Costs*," 22 J. Health Economics 151, 172, 173 (2003). That is a several hundred-fold increase over the post-Hatch-Waxman cost of researching generic drugs, as "the [current] research and development costs for a new generic drug are only 1 to 2 million dollars." ASPE Issue Brief, *supra*, at 4-5.

These costs would be borne by consumers—in the form of increased prices, decreased availability as manufacturers exit the market, or both. Not only does increased generic substitution drive down the price of the *brand* (ASPE Issue Brief, *supra*, at 3), but "[t]he relatively low costs to entry for generic drugs lead to increased competition, which drive prices for

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[4] Only in 2009, and based on a four-year review, did the FDA order a stronger warning regarding the risk of prolonged metoclopramide use. Br. of Petitioners Actavis Inc. et al. 11-12; Br. of Amicus Curiae, *Morris* v. *Wyeth, Inc.*, Doc. 00618908446, No. 09-5509 (6th Cir.) (filed Feb. 5, 2010), and exhibits thereto.

generic drugs down dramatically" too (*id.* at 5). As the FDA has found, "the first [generic] entrant has a relatively small effect on price, but subsequent entrants dramatically reduce the average relative price." *Ibid.* More precisely, "the appearance of a second generic manufacturer reduces the average generic price to nearly half the brand name price. * * * For products that attract a large number of generic manufacturers, the average generic price falls to 20% of the branded price and lower."[8] In short, these plaintiffs do not represent the interest of consumers generally.

Even indulging the assumption that allowing state tort liability might make drugs safer (which is doubtful), Congress has already struck a balance between safety and cost. And where federal law reconciles competing objectives, "that is not a judgment the States may second-guess." *Bonito Boats, Inc.* v. *Thunder Craft Boats, Inc.*, 489 U.S. 141, 152 (1989). Rather, state regulation "must yield to the extent that it clashes with the balance struck by Congress." *Ibid.*; accord *Geier*, 529 U.S. at 874-881 (state tort law was preempted insofar as it balanced competing policy objectives -- including issues of cost and safety—differently from federal law).

Here, state common law regulation would impose substantial costs on generic manufacturers. These costs cannot be brushed aside as extra incentive to comply with federal law; instead, they "would exert an extraneous pull on the scheme established by Congress," and "[are] therefore pre-empted." *Buckman*, 531 U.S. at 353.

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[8] FDA, Generic Drug Prices, http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm129385.htm.

4. Allowing state regulation will impose substantial costs on the FDA.

Finally, from the FDA's side as well, allowing state failure-to-inform-the-FDA claims would impose substantial new costs and create practical problems.

First, due to the risk of second-guessing by juries, companies must "fear that their disclosures to the FDA, although deemed appropriate by the Administration, will later be judged insufficient in state court." *Buckman*, 531 U.S. at 351; see *Geier*, 529 U.S. at 882 ("this Court's pre-emption cases ordinarily *assume* compliance with the state law duty"). And this fear in turn creates "an incentive to submit a deluge of information that the Administration neither wants nor needs, resulting in additional burdens on the FDA's evaluation of an [ANDA]." *Buckman*, 531 U.S. at 351.

More information is not necessarily better. Indeed, the FDA asks drug companies *not* to submit adverse event reports unless there is an identifiable patient and reporter, a suspect drug, and an adverse event—all four—"because reports without such information make interpretation of their significance difficult, at best, and impossible, in most instances."[6] The FDA likewise discourages reporting of adverse events derived from "planned contacts and active solicitation" unless they are "serious" *and* "unexpected"

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[6] Adverse Drug Reaction Reporting Regulations Working Group, Center for Drug Evaluation & Research, *Guidance for Industry, Postmarketing Adverse Experience Reporting for Human Drug & Licensed Biological Products: Clarification of What to Report* 1-2 (Aug. 1997), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071981.pdf.

and "there is a reasonable possibility that the drug or biological product caused the adverse experience." *Id.* at 3-4. The agency even "encourage[s] * * * manufacturers to submit requests to the Agency * * * to waive the requirement to submit [forms] to the FDA for each adverse experience that is determined to be both nonserious and labeled." *Id.* at 4. If state tort law may punish them on a failure-to-inform-the-FDA theory, generic manufacturers are unlikely to comply with such agency requests.

A related problem is that, if the FDA is flooded with unneeded information, then its decision-making will slow down—and it will take even longer for generic drugs to reach consumers. That would be directly contrary to the animating purpose of Hatch-Waxman. Yet delay is already a problem: "Since 2002, the number of ANDAs submitted has continued to grow. [The Office of Generic Drugs] expects that the increased number of ANDAs, plus additional workload from citizen petitions and the submission of ANDAs for more complex drug products, could potentially cause delays in the approval of ANDAs, including ANDAs for drug products that are particularly important to the public health." Center for Drug Evaluation & Research, *Manual of Policies & Procedures* 5240.3, at 1 (Oct. 18, 2006).[7] If allowed to stand, the rulings below will exacerbate this problem.

Further, if state tort liability hinges on hypothetical decisions FDA *might have made*, then FDA will be burdened by demands for discovery regarding internal deliberations and how agency personnel might have responded under various hypothetical scenarios.

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[7] http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm079787.pdf.

Existing regulations suggest that the FDA is not inclined to accommodate such demands. See 21 C.F.R. §§20.1, 20.2(a). But while the Government can resist, parties may challenge any refusal to testify under the APA. *United States ex rel. Touhy* v. *Ragen*, 340 U.S. 462 (1951); *Exxon Shipping Co.* v. *United States Dep't of Interior*, 34 F.3d 774, 778-780 (9th Cir. 1994). Further, if the FDA becomes the gatekeeper for private tort liability, it can anticipate myriad petitions from prospective plaintiffs urging the agency to find unlawful nondisclosures—which would be every bit as burdensome as testifying.

Insofar as the FDA succeeds in beating back such burdens, its reward will be lay juries forced to speculate, without FDA guidance, as to whether the agency would have approved label changes championed after the fact by injured plaintiffs. That is, if state tort liability is allowed to depend on a jury's assessment of what the FDA would have done, the FDA must either submit to the burdens of assessing hypotheticals and participating in private litigation, or we can have no confidence that the jury will reach the right result.

Indeed, while juries will be charged with evaluating the materiality of information not submitted to the FDA, they cannot replicate the FDA process. Congress has directed the agency, in making safety and efficacy determinations, to rely on experts from several scientific disciplines. 21 U.S.C. §355(n). Moreover, juries are ill-equipped to discern how the FDA implements its policies, why certain types of information may be probative (or not probative), or how the agency's institutional expertise affects its evaluation. Thus, while it is questionable whether juries can accurately determine the propriety of warnings at

all,[8] it is frankly absurd to think they can accurately predict what FDA "would have" done.

Finally, the inevitable disconnect between state law and FDA requirements poses serious practical difficulties for generic manufacturers. What is a manufacturer to do if, for example, a jury rules that that it should have provided a new warning that the FDA has not vetted, much less approved? Submit the proposal, to be sure—and pull its product from the market in the meantime? Submit the proposal and ask the FDA to deny it, to preclude liability in other States? And what if the FDA rejects the proposal? It is cold comfort indeed if, in the aftermath of a crippling verdict, the FDA declines to act as the verdict assumes it would have.

CONCLUSION

The decisions below should be reversed and state law failure-to-warn claims against generic drug manufacturers held categorically preempted.

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[8] Fact-finders lack perspective beyond the injured patient in the case before them. See *Carroll* v. *Otis Elevator Co.*, 896 F.2d 210, 215-216 (7th Cir. 1990) (Easterbrook, J., concurring) (jurors in product liability cases tend to focus on "today's injury" rather than probabilities, rendering "invisible" those who would have been harmed had the allegedly defective product *not* been on the market).

Respectfully submitted.

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JANUARY 2011

AMICUS CURIAE BRIEF

Nos. 09-993, 09-1039, & 09-1501

In The Supreme Court of the United States

PLIVA, INC., et al.,

Petitioners,

v.

GLADYS MENSING,

Respondent.

ACTAVIS ELIZABETH LLC,

Petitioner,

v.

GLADYS MENSING,

Respondent.

ACTAVIS, INC.,

Petitioner,

v.

JULIE DEMAHY,

Respondent.

On Writs Of Certiorari To The United States Courts Of Appeals For The Eighth Circuit And For The Fifth Circuit

BRIEF FOR *AMICUS CURIAE* THE NATIONAL COALITION AGAINST CENSORSHIP IN SUPPORT OF RESPONDENTS

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INTEREST OF THE *AMICUS*

The National Coalition Against Censorship (NCAC), founded in 1974, is an alliance of more than 50 national nonprofit organizations, including educational, professional, artistic, labor, religious and civil rights groups united in the conviction that freedom of thought, inquiry and expression are indispensable to a healthy democracy. Among NCAC's projects is The Knowledge Project: Censorship & Science, which educates the public and policy-makers about the importance of safeguarding the free exchange of information about scientific research and developments. The Knowledge Project advocates for greater transparency in government decision-making about science, and for the public's right to know non-classified scientific information, especially when that information implicates public health and welfare. Because the issues in this case relate to the ability of the public to receive truthful information about the risks of pharmaceuticals, participation as *amicus* in this case falls squarely within NCAC's mission. The positions advocated by the NCAC in this brief do not

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Petitioners and Respondents have filed blanket consents to the submission of *amicus* briefs with this Court. No counsel for a party authored any part of this brief, and no such counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than *Amicus curiae*, or its members, or counsel, made a monetary contribution to its preparation or submission.

necessarily reflect the positions of each of its participating organizations.

SUMMARY OF ARGUMENT

Petitioners' argument boils down to their contention that, in enacting the Hatch-Waxman Amendments to the Food, Drug, and Cosmetic Act ("FDCA"), Congress chose to permit name-brand manufacturers unilaterally to revise their labels and issue warnings to patients and the medical community, but prohibited generic drug manufacturers from doing the same. Petitioners' argument, however, conflicts with this Court's First Amendment jurisprudence which has recognized that the First Amendment "prohibit[s] . . . restrictions distinguishing among different speakers, allowing speech by some but not others." *Citizens United v. Federal Election Comm'n*, 130 S.Ct. 876, 898-99 (2010); *see also First Nat. Bank of Boston v. Bellotti*, 435 U.S. 765, 784 (1978).

Whether "warnings" are deemed to be pure or commercial speech, Petitioners have a First Amendment right (whether actually exercised or not) to utilize a host of mediums to inform the public and medical community about the risks associated with their products. Indeed, in their opening brief, Petitioners Pliva, Inc., Teva Pharms. USA, Inc. and UDL Labs, Inc. (collectively "Pliva") readily concede they have a First Amendment right to engage in truthful speech and concede that any Governmental attempts

to chill such speech would be unconstitutional. *See* Pliva Opening Br. at 48.

Simply put, nothing in the Food, Drug and Cosmetic Act ("FDCA") ***precluded*** Petitioners from issuing additional warnings, even without FDA approval. *See* 21 C.F.R. §§ 200.5, 201.80, 314.70(c) and 314.97. Even assuming for the sake of argument, that such a statutory preclusion existed, Petitioners' would still have the right under the First Amendment to disclose known risks about their products. Conflict preemption principles do not apply if there is no conflict between federal and state law. Under the First Amendment Petitioners have a right to issue additional warnings about known risks, and under state law, they have the duty to do so. There is no conflict between state and federal law.

ARGUMENT

In *Levine*, this Court confirmed that name-brand drug manufacturers bear the primary responsibility for their label and are permitted to unilaterally issue more robust warnings than those initially approved by the FDA. *Wyeth v. Levine*, 129 S.Ct. 1187, 1198-99 (2009). Petitioners argue that, while name-brand manufacturers are free to unilaterally make labeling changes, generic manufacturers are not free to make any changes or disseminate any stronger warnings than those provided by the name-brand manufacturer and approved by the FDA. They argue that, because

their label matched the name-brand manufacturers' label, Respondents' claims are preempted. There are a number of reasons for rejecting Petitioners' preemption arguments. These include, *inter alia*: the basic presumption against preemption; the power of drug companies, pursuant to the Changes Being Effected ("CBE") statute, to issue additional warnings without pre-approval by the FDA (see, *e.g.*, 21 C.F.R. §§ 314.70(c) and 314.97); Petitioners' right to issue "Dear Doctor" letters to physicians regarding the risks; and Petitioners' failure to present clear evidence that the FDA would not have approved a labeling change. These issues were all carefully considered by the Fifth and Eighth Circuits in their respective opinions and are addressed in Respondents' principal brief. This brief is intended to focus on one narrow aspect of Petitioners' conflict preemption argument: Petitioners' First Amendment right to disseminate warnings about known risks through labeling revisions, "Dear Doctor" letters and scientific journal articles.[1]

Like all other federal laws and regulations, the FDCA and the FDA regulations must be interpreted in a manner consistent with the Free Speech Clause of the First Amendment. *Thompson v. Western States Medical Center*, 535 U.S. 357, 365 (2002). "Scientific and academic speech resides at the core of [the] First

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[1] The brief addresses only the First Amendment right to disseminate information that is concededly truthful and not misleading. Other situations involving disputed facts might pose different legal questions that this brief does not address.

Amendment." *Washington Legal Foundation v. Friedman*, 13 F.Supp.2d 51, 62 (D.D.C. 1998) ("*WLF I*"), vacated as moot by, *Washington Legal Foundation v. Henney*, 202 F.3d 331, 337, n.7 (D.C.Cir. Feb 11, 2000) ("*WLF III*"); *see also Board of Trustees of Leland Stanford Junior University v. Sullivan*, 773 F.Supp. 472, 474 (D.D.C. 1991) ("It is equally settled, however, though less commonly the subject of litigation, that the First Amendment protects scientific expression and debate just as it protects political and artistic expression.").

In these consolidated cases, Respondents allege that Petitioners should have issued warnings about a known risk, that long term use of metoclopramide increases the risk of tardive dyskinesia. The dissemination of such "factual material of clear 'public interest'" is entitled to First Amendment protection. *Bigelow v. Virginia*, 421 U.S. 809, 822 (1975). Petitioners' argument that the Government permits name-brand manufacturers to unilaterally issue warnings but prohibits generic manufacturers from doing the same, creates a colossal First Amendment problem – under the First Amendment, Government cannot distinguish among different speakers. *Citizens United*, 130 S.Ct. at 898-99. Moreover, in addition to the impermissible restrictions based on the identity of speakers, Petitioners have an independent (and self-admitted) First Amendment right to provide information that serves the goals of the FDA regulations: informing consumers of known risks of pharmaceutical. *See, e.g.*, Pliva's Br. at 48; *Thompson*, 535 U.S. at 365.

I. Under The First Amendment, Congress Cannot Discriminate Among Different Speakers.

Petitioners readily concede that, under FDA regulations, name-brand manufacturers of Reglan (metoclopramide) can, without prior FDA approval, *unilaterally* issue warnings through labeling revisions or "Dear Doctor letters" regarding risks associated with Reglan use. *See* Pliva's Br. at 16. They contend, however, that these same FDA regulations *prohibit* generic manufacturers of the same drug from unilaterally issuing warnings. *Id.* at 30-47. In sum, they contend that, through the Hatch-Waxman Act, Congress sought to make name-brand manufacturers the favored speaker and made it criminally illegal for generic manufacturers to issue warnings in advance of the name-brand manufacturer and without the FDA's consent.

Petitioners' (and the Government's) position that name-brand manufacturers are free to issue unilateral warnings but generic manufacturers are not, is a violation of the First Amendment. In *Citizen's United*, this Court held:

> [T]he First Amendment stands against attempts to disfavor certain subjects or viewpoints. Prohibited, too, are restrictions distinguishing among different speakers, allowing speech by some but not others.

Citizen's United, 130 S.Ct. at 898-99. Accordingly, even assuming for the sake of argument that the Hatch-Waxman Act places speech restrictions

distinguishing amongst name-brand and generic manufacturers, such restrictions would not survive First Amendment scrutiny. *Id.*

Moreover, such a restriction would deny consumers access to potentially life-saving information regarding the proper use and risks associated with their drugs, a result that is wholly inconsistent with the FDA's mission. Given that generic manufacturers have the ongoing duty to record and report adverse events to the FDA (21 C.F.R. § 314.98(a)), it would be anomalous if they were prevented from informing the medical community regarding the risks they observe. Finally, in many instances, name-brand manufacturers have divisions within their companies or subsidiaries which manufacture generic drugs.[3] Thus, it makes no sense for Congress to hold that, when the manufacturer is wearing its name-brand hat, it is free to issue warnings, but, when this same manufacturer is wearing its generic-brand hat, it is prohibited from issuing warnings.

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[3] During hearings on the Hatch-Waxman Act, Congress learned that name-brand manufacturers were also producing generic drugs, which led Congressman Dennis Eckart to ask "So the big boys are playing both sides of the field on this?" Mark Novitch, M.D., the Deputy Commissioner of the FDA responded in the affirmative ("Yes . . . "). *See Drug Legislation: Hearings Before the Subcommittee on Health and the Environment of the House Committee on Energy and Commerce*, 98th Cong. (July 25, 1983). This practice continues in the modern era. For example, Sandoz Inc., one of the world's largest generic drug manufacturers is a generic drug subsidiary of Novartis Pharmaceuticals Corporation, a multi-national name-brand manufacturer.

In sum, Petitioners and the Government's argument that name-brand manufacturers are free to speak/warn the public and that generic manufacturers are restricted from doing so places an unconstitutional restriction upon generic manufacturers' and the public's First Amendment rights. *Citizen's United*, 130 S.Ct. at 882-83, 908 (First Amendment prohibits Congress from distinguishing amongst speakers); *Virginia State Bd. of Pharmacy v. Virginia Citizens Consumer Council, Inc.*, 425 U.S. 748, 757 (1976) (First Amendment protects the public's right to *receive* information). As this Court has aptly observed:

> When Government seeks to use its full power, including the criminal law, to command where a person may get his or her information or what distrusted source he or she may not hear, it uses censorship to control thought. This is unlawful. The First Amendment confirms the freedom to think for ourselves.

Citizen's United, 130 S.Ct. at 908. Accordingly, Petitioners contention that Congress sought to discriminate amongst manufacturers is neither supported by the Act nor permissible under the First Amendment.

II. The First Amendment Protects The Right Of All Drug Companies To Disclose Information About The Known Risks Associated With Their Products.

In addition to the impermissible discriminatory aspects outlined *supra*, Petitioners also have an *independent* First Amendment right to warn the public if they become aware of previously undisclosed risks. Respondents allege that Petitioners could and should have issued warnings regarding the known risks of tardive dyskinesia from long term use of metoclopramide, and that the failure to do so constituted negligence. The dissemination of "factual material of clear 'public interest'" is entitled to First Amendment protection. *Bigelow v. Virginia*, 421 U.S. 809, 822 (1975). The degree of protection is determined by whether warnings are deemed *pure speech* (which is afforded the highest level of protection) or if it is "*commercial speech*" (in which case it is entitled to a lower level of protection). However, irrespective of whether the warnings are deemed to be "pure speech" or "commercial speech," the First Amendment would nonetheless protect Petitioners' right to issue warnings in the present case.

(A) More Robust Warnings Than Those Contained In The FDA-Approved Label Constitute Pure, Not Commercial, Speech And Are Subject To The Most Extensive First Amendment Protection.

Warnings concerning drug risks constitute pure speech. Warnings are not given in order to enhance the sale of a product, rather, they tend to limit product sales. As such, warnings do not fall within the ambit of "commercial" speech. Even if, as Petitioners claim, FDA regulations preclude issuance of such warnings, they would be a content-based restriction on Petitioners' ability to speak and would be subject to "strict scrutiny."

Whether a given communication constitutes commercial speech is predicated on "the commonsense distinction between speech proposing a commercial transaction . . . and other varieties of speech." *Bolger v. Youngs Drug Products Corp.*, 463 U.S. 60, 64 (1983). In *Bolger*, this Court identified three factors to use in determining whether speech is "pure" speech or "commercial" speech: (1) Whether the speech is concededly an advertisement; (2) Whether the speech refers to a specific product; and, (3) Whether the speaker has an economic motivation for disseminating the speech. *Bolger*, at 66. If ***all three factors*** are present, the speech may properly be characterized as commercial speech. *Id.*; *see also WLF I*, 13 F.Supp.2d at 64.

On a common sense level, a more robust warning of the risks of an approved drug does not comport with the *Bolger* test for commercial speech. After all, an advertisement "calls public attention to [the product], especially by emphasizing desirable qualities so as to arouse desire to buy or patronize." *WLF*, 13 FSupp.2d at 64. A warning about the risks in using an approved drug in a particular manner does exactly the opposite: It ***de***emphasizes the desirable qualities of the drug and emphasizes its ***un***desirable qualities. Similarly, a warning that highlights the risk of using a drug is an economic ***dis***incentive, and does not comport with the third *Bolger* factor because there is no economic motivation for disseminating the speech.

Because more robust warnings about the use of an approved drug are "pure" (as opposed to "commercial") speech, any content-based restriction is subject to the strict scrutiny standard. *Sable Communications of California, Inc. v. FCC*, 492 U.S. 115, 126 (1989); *United States v. Playboy Entertainment Group, Inc.*, 529 U.S. 803, 813-14 (2000). Where a statute regulates speech based on content, the statute "must be narrowly tailored to promote a compelling government interest." *Playboy*, 529 U.S. at 813. Moreover, to the extent Petitioners argue they could not disseminate more robust and truthful warnings about the use of their product without prior FDA approval, or without the name-brand manufacturer's initiation, such a limitation would amount to a "prior restraint" on protected expression – which is the most serious and least tolerable infringement on First Amendment

rights. *Organization for a Better Austin v. Keefe*, 402 U.S. 415, 419 (1971); *see also The Florida Star v. B.J.F.*, 491 U.S. 524, 533 (1989).

The FDA could not possibly assert a compelling governmental interest in keeping physicians and patients in the dark about the risks associated with the drugs they are using. Such a conclusion would, in fact, be directly contrary to the FDA's mandate that it promote and enhance consumer ***safety***. *Levine*, 129 S.Ct. at 1195-96; *United States v. Dotterweich*, 320 U.S. 277, 282 (1943); *Demahy v. Actavis, Inc.*, 593 F.3d 428, 448 (5th Cir. 2010) ("Hatch-Waxman's goals are thus tethered to those of the overall regulatory scheme – chief among them the maintenance of safety and efficacy"). The First Amendment assures that truthful speech that makes the use of drugs ***safer*** cannot be limited by the FDA's regulatory scheme.

Today, seventy percent of prescriptions are filled with generic drugs. *Mensing v. Wyeth, Inc.*, 588 F.3d 603, 607 (8th Cir. 2009); *see also* Susan Okie, *Multinational Medicines – Ensuring Drug Quality in an Era of Global Manufacturing*, 361 NEW ENG. J. MED. 737, 738 (2009). Many insurance companies only pay for generic drugs which forces patients to use generic drugs. It is, thus, all the more important that generic manufacturers warn patients and doctors about side effects once they become aware of them. *See Demahy*, 593 F.3d at 448 ("nothing about the Hatch-Waxman Amendments, and their goal of cheaper drugs, obviates the concomitant prescription that all drugs, even cheaper ones, remain safe.")

To hold that FDA regulations prohibited Petitioners' disclosure of safety risks would mean that the public would be deprived of vital health and safety information in a timely fashion. If FDA regulations operated in such a fashion, it would constitute a content-based restriction speech, which is the type of evil the First Amendment was meant to prevent. *Washington Legal Foundation v. Henney*, 56 F.Supp.2d 81, 85 (D.D.C. 1999) ("*WLF III*") ("The First Amendment is premised upon the idea that people do not need the government's permission to engage in truthful, nonmisleading speech about lawful activity.") As such, under strict scrutiny, Petitioners' argument that the government has a compelling interest in preventing disclosure of known health risks must fail.

(B) Even If Warnings Were Deemed Commercial Speech, Petitioners Still Have A Right To Disclose Them.

Even if additional warnings were deemed "commercial speech," Petitioners have a First Amendment right to publish information about the risks of using their drugs. *Thompson*, 535 U.S. at 365. In *Thompson*, this Court struck down a ban on advertising unapproved compounded drugs in the FDA Modernization Act of 1997 (FDAMA). The Court applied the commercial speech test of *Central Hudson v. Gas & Electric Corp. v. Public Serv. Comm'n*, 447 U.S. 557 (1980). Thus, this Court asked: (1) whether the speech was untruthful or misleading, or concerned unlawful

activity (characteristics that would strip the speech of First Amendment protection and end the analysis); (2) whether the Government had asserted a "substantial" interest in restricting the speech; (3) whether the Government had demonstrated that the restriction "directly advanced" such a substantial interest; and (4) whether the Government had established that the restriction was "not more extensive than is necessary to serve that interest." *Thompson*, 535 U.S. at 365.

1. Issuing Warnings Is Neither Unlawful Nor Inherently Misleading.

Respondents allege that truthful additional warnings about the use of metoclopramide were necessary for the protection of the Respondents' health and safety. Petitioners argue they could not issue such warnings without first waiting for the name-brand manufacturers to act or obtaining the FDA's approval. However, it is illogical to assume that speech about known drug-related risks is "inherently misleading" if it has not been specifically endorsed by the FDA, especially when the speech at issue further advances the FDA's statutory goals.

In the context of prescription drugs, the theory that statements lacking FDA approval were inherently misleading was considered and rejected in *WLF I*. There, the FDA argued that manufacturer-funded or manufacturer-disseminated speech about off-label uses was inherently misleading. The court held that the speech was "*not untruthful or inherently misleading*

merely because the FDA has not yet had the opportunity to evaluate the claim." Id.

In short, Petitioners' argument that warnings about known risks discovered after FDA approval of the label are "inherently misleading" is untenable. Indeed, drug manufacturers are required to report post-marketing data about adverse drug effects precisely so that patients and doctors have the benefit of the most up to date information about drug-related risks.

2. The FDA Does Not Have A "Substantial" Interest In Keeping People In The Dark Regarding Known Risks Associated With The Prescription Drugs That They Use.

It is not disputed that government agencies may seek to regulate speech for certain legitimate purposes. However, the FDA does not have a substantial interest in keeping physicians and consumers in the dark regarding life endangering or serious risks associated with the drugs that consumers use. Such a conclusion would, in fact, be directly contrary to the FDA's mandate that it promote and enhance consumer safety. *Levine*, 129 S.Ct. at 1195-96; *see also Dennaly*, 593 F.3d at 448 ("Hatch-Waxman's goals are thus tethered to those of the overall regulatory scheme – chief among them the maintenance of safety and efficacy").

3. The Purported Restrictions On Speech Do Not Advance The Government's Substantial Interest In Protecting The Health And Safety Of Consumers.

This Court has repeatedly confirmed that the role of the FDCA and the FDA is to protect consumers. *Levine*, 129 S.Ct. at 1195-96; *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120 (2000) ("The labeling requirements currently imposed by the FDCA . . . require the FDA to regulate the labeling of drugs and devices to protect the safety of consumers."); *United States v. Sullivan*, 332 U.S. 689, 696 (1948) ("[T]he Act as a whole was designed primarily to protect consumers from dangerous products.").

In light of the fact that the FDCA's primary objective is to protect consumers, that objective and interest would be undermined by Petitioners' contention that the FDA could or should prohibit warnings about the known risks of their products. *See, e.g., Dotterweich*, 320 U.S. at 282; *Levine*, 129 S.Ct. at 1195-98. The more information a physician has when prescribing a drug, the better. *See* American Medical Association, *Reporting Adverse Drug and Medical Device Events: Report of the AMA's Council on Ethical and Judicial Affairs*, 49 FOOD & DRUG LAW JOURNAL 359, 363 (1994) ("The purpose of any requirement to disseminate knowledge is to benefit patients and advance their level of care."). If the regulations were construed to restrict distribution of information about health risks, such a construction would undermine FDA's interest in promoting access to reliable scientific

and medical information and would thereby endanger the lives of patients who are prescribed medications.

This Court's First Amendment jurisprudence has long mandated that government cannot suppress truthful information – even when that information does nothing more than allow them to make better *financial* judgments about what they buy. *Virginia State Bd. of Pharmacy*, 425 U.S. at 770; *44 Liquormart, Inc. v. Rhode Island*, 517 U.S. 484, 503 (1996); *Thompson*, 535 U.S. at 365. It is far more important that these First Amendment principles apply to assure that patients and their physicians have truthful information that will assist them in choosing drug products that affect consumers' health and safety and not merely their pocketbooks. An FDA regulation that limits the dissemination of truthful warnings undermines patient safety, is contrary to governmental intent and violates the First Amendment.

4. A Restriction On Warnings Is More Extensive Than Necessary.

Finally, as to the fourth factor, Petitioners' contention that the FDA does or should bar all additional warnings (including Dear Doctor letters) by generic manufacturers until approved by the FDA is more extensive than necessary because it burdens substantially more speech than necessary. *U.S. v. Edge Broadcasting Co.*, 509 U.S. 418, 430 (1993). First, as already noted, such a restriction would be an

unnecessary and unconstitutional prior restraint. *See, e.g.*, *WLF II*, 56 F.Supp.2d at 85. Second, as the *WLF I* court noted, in lieu of prohibiting speech, the FDA could require "full, complete, and unambiguous disclosure by the manufacturer." *WLF I*, 13 F.Supp.2d at 73. Finally, as the *WLF I* court noted, the FDA cannot restrict the dissemination of truthful information, especially when the "truthful information may be life saving information." *WLF I*, 13 F.Supp.2d at 73. Truthful warnings are exactly the type of life-saving information that cannot be restricted and are fully protected by the First Amendment.

The FDA has long understood that completely suppressing the exchange of accurate scientific and medical information between physicians and the manufacturers of drugs and devices does not serve its public health objectives. For example, in the context of permitting drug manufacturers (both name brand and generic) to publish journal articles regarding off-label[*] (unapproved) drug uses, the FDA stated in 1994 that, "because the agency recognizes the importance of dissemination of reliable scientific information . . . , it has developed a number of policies related to dissemination of such information." 59 Fed.

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[*] "Off-label" refers to the use, prescription or marketing of an FDA-approved drug for an unapproved use, such as in an unapproved population (i.e., children) or for a condition other than for what it has been approved. *See, e.g.*, *Kruger v. SmithKline Beecham*, 583 F.Supp.2d 553, 572, n. 21 (E.D.Pa. 2008).

Reg. 59820, 59822 (Nov. 18, 1994). In its more recent pronouncement on this issue, the FDA confirmed that manufacturers have a right to "disseminate truthful and non misleading medical journal articles and medical or scientific reference publications on unapproved uses of approved drugs . . . to healthcare professionals." *See* FDA, *Guidance for Industry — Good Reprint For The Distribution Of Medical Journal Articles And Medical Or Scientific Reference Publications On Unapproved New Uses Of Approved Drugs And Approved Or Cleared Medical Devices* (January 2009), available at http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm (last visited February 28, 2011). The FDA further held that, along with the dissemination of such information, the manufacturer should also disclose "*all significant risks or safety concerns known to the manufacturer* . . ." *Id.* Thus, contrary to the Petitioners' contention, they were not only permitted but *encouraged* to disclose any known safety problems with their drugs. For this reason alone, Petitioners' preemption argument should be rejected.[5]

Accordingly, under the First Amendment, Petitioners had a right to issue truthful additional warnings about the risks associated with prolonged use of metoclopramide.

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[5] Rejecting Petitioners' preemption argument would have the added benefit of recognizing the state's legitimate interest in protecting its citizens from negligence through application of state tort law.

III. To Avoid Constitutional Doubt, The Hatch-Waxman Act And FDA Regulations Should Be Interpreted To Allow Generic Manufacturers To Issue Additional Warnings.

Statutes, and the regulations drafted pursuant to them, must be interpreted so as to avoid constitutional doubt. *Muller v. French*, 530 U.S. 327, 336 (2000); *Almendarez-Torres v. U.S.*, 523 U.S. 224, 237-38 (1998). Petitioners claim that the Hatch-Waxman Act and applicable FDA regulations prohibited them from unilaterally making labeling changes. However, as discussed *supra*, as well as in Respondents' brief, nothing within the Act or the regulations supports Petitioners' arguments that Congress intended to prevent generic manufacturers from revealing risks discovered post-approval. Indeed, the applicable regulations confirm that Petitioners were free to issue warnings and make labeling changes. *See* 21 C.F.R. §§ 200.5, 201.80, 314.70(c) and 314.97.

More importantly, Petitioners' construction of the regulations violates the rule that a regulation must be construed in a manner that resolves any doubt against unconstitutionality. Construction of the regulation in the manner suggested by Petitioners raises constitutional concerns to the extent it would prohibit dissemination of information of hazards that have long been known, but secreted by the manufacturer for whatever reason.

IV. Because Petitioners Have A First Amendment Right To Notify Patients And Doctors About Known Risks Associated With Their Product, They Could Comply With State Law Requiring Such Warnings.

Petitioners' challenge to the Fifth and Eighth Circuit Courts' decisions is predicated solely on principles of conflict preemption. Petitioners assert they could not comply with both federal law (which, Petitioners contend, precluded warnings about known risks) and state law (which required such warnings).

But, as demonstrated above, the First Amendment protects Petitioners' right to disseminate warnings about known risks associated with the use of their drugs, even if such warnings were not contained in the FDA-approved name-brand label, regardless of whether they chose to exercise that right. Because federal law did not restrict the warnings Petitioners could issue, Petitioners could have complied with state law and issued the warnings, had they chosen to do so. There was no conflict and, hence, no conflict preemption. Tellingly, Petitioners themselves acknowledge they have First Amendment rights to engage in speech. *See, e.g.*, Pliva Br. at 48. However, they contend that, because it is "speculative" as to what the FDA would have done in response to their exercise of their First Amendment rights, Respondents' claims should be preempted. *Id.* at 48-49. Petitioners fail to appreciate that, under *Levine*, they bear the burden of establishing preemption by presenting "clear evidence that the FDA would not have approved a

change to . . . [the] label" *see Levine*, 129 S.Ct. at 1198 – thus, their contention that the FDA's actions are "speculative" confirms that they cannot meet the demanding standard espoused in *Levine*. *Levine*, 129 S.Ct. at 1198; *see also Mensing v. Wyeth, Inc.*, 588 F.3d 603, 610 (8th Cir. 2009) ("the Supreme Court made it clear in [*Levine*] that uncertainty about the FDA's response to such measures makes federal preemption less likely"); *Dorsett v. Sandoz, Inc.*, 699 F.Supp.2d 1142, 1159 (C.D.Cal. 2010) ("a mere possibility that the FDA might not have allowed an enhanced warning . . . is not enough to warrant preemption.")

Petitioners may argue that, even if the First Amendment ***allowed*** them to issue additional warnings, the First Amendment also allows them to remain silent. That is true, but misses the point. They could remain silent, however that choice would violate a duty under state law and expose them to potential liability. The point is that the state law duty is not in conflict with any federal limitation because, in fact, there is no federal limitation.

The question is this: Can a manufacturer with knowledge of a grave risk associated with its drug issue a warning to the medical community regarding that risk? Petitioners' argument that federal law prohibits them from issuing such a warning is simply wrong. Petitioners were aware of the substantial risks associated with long term metoclopramide use yet chose not to disclose it to patients and doctors. Petitioners had both a state law duty and a First

Amendment right to issue a warning regarding such risks without waiting for the FDA's confirmation or name-brand manufacturer's inclusion of the warning. Petitioners were not put to the test of choosing between compliance with state and federal law. The federal regulations do not in fact prohibit enhanced warnings reflecting current knowledge and, if they were so construed, such a construction would run afoul of the First Amendment. Petitioners could, therefore, comply with both federal and state law.

CONCLUSION

Our independence was won by those who believed public discussion and free speech should be a fundamental principle of the American government. They recognized that it is hazardous to discourage thought, innovation and debate. They knew the path of safety lies in the opportunity to discuss freely. Believing in the power of reason as applied through public discussion, our forefathers eschewed silence coerced by law.[5] Contrary to the fundamental beliefs of our forefathers, today, Petitioners claim they are prohibited from publicly disclosing risks associated with their drugs – contending they are not free to update warnings on labels, not free to send letters to

[5] This history was more eloquently outlined in Justice Brandeis' concurring opinion in *Whitney v. California*, 274 U.S. 357, 375-76 (1927), *overruled on other grounds by Brandenburg v. Ohio*, 395 U.S. 444 (1969).

physicians, and ostensibly not free to publish articles or letters in scientific journals revealing these grave risks. Petitioners' self-serving asseverations ring hollow. Had it been in their financial interest to disclose the information, they undoubtedly would have claimed the First Amendment right to do so. Instead, they seek to justify concealing information about risk and to avoid any legal consequences for injuries that resulted. First Amendment jurisprudence requires rejection of Petitioners' argument that they were precluded from issuing warnings to inform consumers and doctors about the known risks of using their products.

Respectfully submitted.

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AMICUS CURIAE BRIEF

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PLIVA, INC., ET AL., PETITIONERS

v.

GLADYS MENSING, RESPONDENT

ACTAVIS ELIZABETH, LLC, PETITIONER

v.

GLADYS MENSING, RESPONDENT

ACTAVIS INC., PETITIONER

v.

JULIE DEMAHY, RESPONDENT

ON WRITS OF CERTIORARI TO THE UNITED STATES COURTS OF APPEALS FOR THE EIGHTH AND FIFTH CIRCUITS

BRIEF FOR THE NATIONAL CONFERENCE OF STATE LEGISLATORS AS *AMICI CURIAE* IN SUPPORT OF RESPONDENTS

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Statement of Interest*

Amicus the National Conference of State Legislatures (NCSL) is a bipartisan organization that serves the legislators and staffs of the Nation's 50 States, its commonwealths and territories. NCSL provides research, technical assistance, and opportunities for policymakers to exchange ideas on the most pressing state issues. NCSL advocates for the interests of state governments before Congress and federal agencies, including the Food and Drug Administration (FDA), and it regularly submits briefs amicus curiae to this Court in cases that raise issues of vital state concern.

In *Wyeth v. Levine*, 129 S. Ct. 1187 (2009), this Court held that the federal regulatory regime governing pharmaceuticals does not preempt state law failure-to-warn claims against the manufacturer of a brand name drug. Petitioners here claim that various federal regulations relating to generic drugs should be interpreted to preempt traditional state law remedies as to manufacturers of generic drugs. Like *Wyeth*, in which NCSL submitted a brief opposing preemption, this case implicates several areas of core concern and special expertise for NCSL, its members, and their respective States.

The state interests implicated here are many and vital. The formulation of public policy on health

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* Pursuant to Supreme Court Rule 37.6, amicus affirms that no counsel for a party authored this brief in whole or in part and that no person other than amicus and its counsel made a monetary contribution to its preparation or submission. All parties' letters consenting to the submission of amicus briefs have been filed with the Clerk's office.

care, insurance, safety, and welfare, including regulation of medicine and pharmacy, have historically been the responsibility of the States. Consumer protection and providing means of redress for personal injuries have also been the province of state legislatures and courts.

State legislatures have decades of experience with the issues most directly implicated in this case. Even before the 1984 Hatch-Waxman Amendments to the Food, Drug and Cosmetic Act (FDCA), States were at the forefront of efforts to control public and private health care costs through policies aimed at increasing the availability and public acceptance of generic drugs. Moreover, state legislatures across the country have considered and enacted significant civil justice reform measures, carefully weighing complaints about the fairness, predictability and efficiency of liability rules. While different States have taken different approaches, these efforts typically represent serious efforts to reconcile important state interests in promoting safety and providing redress with reducing litigation and health care costs.

States have a strong interest in vindicating the presumption against preemption and the presumption's corollary: that, consistently with the Constitution, decisions to oust States from areas of their traditional authority, even when fully within Congress's powers, should be made by Congress. Not only is that the branch of government in which States enjoy representation, but neither courts nor administrative agencies are as well-equipped to evaluate the complex, competing policy considerations that preemption questions typically present.

Indeed, this case vividly illustrates the reasons for adhering to the constitutional allocation of policymaking authority – and the dangers of free-form judicial or administrative preemption.

SUMMARY OF ARGUMENT

The plea at the heart of this case fails for the same reason as the one rejected in *Wyeth*: the absence of any showing that Congress intended to divest States of their historic power to provide a remedy against those whose defectively marketed products caused injury. Federalism is not only a principle, but a system of government: As mentioned, providing compensation for injured citizens and regulating health care professions are not merely areas where the States claim jurisdiction by tradition, but ones where they have responsibilities that federal authorities do not share.

This Court's precedents counsel great hesitation before accepting claims of implied preemption, and for good reason. Implied preemption based upon penumbras and emanations from federal regulation, and facile claims of federal administrative inconvenience, deprives States of their best, constitutionally promised means of upholding their duly enacted policies: their representation in Congress. In this case, the argument against preemption is overwhelming because Congress displayed no intent to disturb States' longstanding and complementary role. Petitioners' claims of "irreconcilable conflict" are painfully thin and are disavowed by the agency on whose behalf they are ostensibly asserted.

Under the regime petitioners advocate, an individual prescribed the same drug bearing the same inadequate warning and injured thereby will be denied recourse – either because the pharmacist elected to fill the prescription with a generic drug, or because the insurer or State's Medicaid law provides for or insists on generic substitution. Such a rule would unsettle bedrock assumptions that have guided state law in this field for decades. All of the States have adopted carefully drawn policies on generic substitution, which encourage and often require the dispensing of generic drugs except where the patient has a specific medical need for the brand drug. These policies have been a major factor in expanding demand for generic drugs. The bizarre, disparate liability regime for brand and generic drugs that petitioners posit would put both health care providers and patients in a quandary and would cause the confusion and reluctance to accept bioequivalent drugs that petitioners claim are critical federal concerns.

In the absence of any indication that Congress intended such a regime, petitioners advance arguments based on *Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341 (2001), and *Arkansas Louisiana Gas Co. v. Hall*, 453 U.S. 571 (1981) (*ArkLa*), to the effect that tort duties of care are incompatible with the FDA's exercise of its statutory responsibilities. *Buckman* has little if any relevance to this case. As the *Wyeth* Court explained in rejecting a similar *Buckman*-based argument, claims based upon traditional common law duties do not resemble the novel "fraud on the FDA" third-party claim at issue in *Buckman*.

ArkLa and *Chicago & North Western Transportation Co. v. Kalo Brick & Tile Co.*, 450 U.S. 311 (1981), are no more helpful. Like *Buckman*, both cases entailed attempts to have a state court overturn a particular federal agency decision on a matter within the core of the agency's jurisdiction. Here, petitioners do not attack any FDA decision, and the agency's approval of an abbreviated new drug application (ANDA) or its corresponding label is not a determination that warnings are adequate for all time. On the contrary, consistent with the common law, the agency requires that warnings be modified as new risk information develops. Indeed, for reasons *Wyeth* highlighted, the regime here is nearly the opposite of the "filed rate" approach to utility rate regulation at issue in *ArkLa*. Tort liability gives regulated parties practical incentives to take actions – updating warnings to reflect new information – that serve core federal safety objectives. Those same objectives would be undermined by a "filed-rate" type rule requiring adherence to outdated warnings no matter what the circumstances.

Equally unavailing are petitioners' efforts to derive general preemption principles claim from broad *language* in the *Buckman* and *ArkLa* opinions. They worry that state law might "skew" a tacit federal balance; that a federal standard may be a ceiling rather than a floor; or that state law might lead to unwelcome burdens on federal regulators. But such amorphous concerns are less arguments for preemption here than for unrestricted preemption everywhere, including anywhere the federal government has acted or could have, but did not.

ARGUMENT

I. BROAD CLAIMS OF IMPLIED PREEMPTION LIKE THOSE ADVANCED HERE ARE INCONSISTENT WITH OUR CONSTITIONAL FRAMEWORK AND THREATEN TO UNDERMINE STATE GOVERNMENT AND ADMINISTRATION

The preemption plea at the heart of this case is in every way extraordinary. Petitioners do not identify any statutory basis for preemption. Nor do they seriously argue that Congress considered displacing any state law, including traditional state common law remedies, in enacting the FDCA or the Hatch-Waxman Amendments. Rather, petitioners invite the Court to invalidate the laws of fifty States and upset decades of state-level policymaking based on a claimed "conflict" between the common law duties and a disputed agency interpretation of certain of its regulations – indeed, one for which the agency itself disclaims preemptive intent or effect.

Under the Constitution and this Court's precedents, such claims warrant severe skepticism. Precisely because the Constitution limits the power to displace state law to "laws of the United States," *i.e.*, acts that have withstood a carefully crafted legislative process hedged with safeguards for "States *qua* States," such claims must clear "a high threshold." *Gade v. Nat'l Solid Wastes Mgmt. Ass'n*, 505 U.S. 88, 110 (1992) (Kennedy, J., concurring). A lesser standard would undercut "the principle that it is Congress rather than the courts that pre-empts state law." *Id.* at 111. *See also Louisiana Pub. Serv. Comm'n v. FCC*, 476 U.S. 355, 374 (1986) ("[A]n agency literally has no power to act, let alone pre-

empt the [law] of a sovereign State, unless and until Congress confers power upon it."); *cf. Alexander v. Sandoval*, 532 U.S. 275, 291 (2001) (with "implied" rights of action, "[a]gencies may play the sorcerer's apprentice but not the sorcerer himself").

Indeed, insistence on a congressional warrant for preemption takes on greater significance as judicial enforcement of limits on federal power has ebbed, and the federal government has not only claimed, but pervasively exercised, authority in numerous areas previously left to the States. *See Gregory v. Ashcroft*, 501 U.S. 452, 464 (1991) ("[I]nasmuch as this Court in *Garcia* [*v. San Antonio Metropolitan Transit Authority*, 469 U.S. 528, 550-54 (1985)], has left primarily to the political process the protection of the States against intrusive exercises of Congress' Commerce Clause powers, we must be absolutely certain that Congress intended such an exercise."); *Wyeth*, 129 S. Ct. at 1205-17 (Thomas, J., concurring in the judgment).

It is telling that petitioners' amici assert that "only the FDA can see the whole picture." Generic Pharm. Ass'n Br. 27-28. But such faith in the peripheral vision of federal administrators is misplaced. Single-subject administrative agencies are not empowered to consider, let alone act upon, the broad range of interests and perspectives state legislatures must weigh. For example, in this case, it is undisputed that compensation for persons injured by prescription drugs is simply not within the FDA's mandate.[1]

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[1] Thus, while the FDA regularly adverts to its reluctance to intrude on the "practice of medicine" as a reason broadly to allow off-label uses of drugs, it is States

Indeed, all too often, federal agencies have scant interest in seeing as much of "the whole picture" as they could. NSCL's amicus brief in *Wyeth* described a stark example: Although Executive Order 13,132 ("Federalism") (Aug. 4, 1999) requires in the plainest terms that every agency provide to "all affected State and local officials" advance notice, and appropriate opportunity to be heard, whenever they "propose[] to act through adjudication or rule-making to preempt State law," the FDA had afforded no consultation and prepared no "federalism impact statement" for the 2006 regulatory preamble considered in *Wyeth*. This preamble had purported, for the first time, to preempt tort suits against drug manufacturers. *See* NCSL Br. 2 (explaining that NCSL Executive Branch Liaison had requested, but had been denied a copy of the proposal, on which the FDA accepted comments from industry groups); *see also* Nina A. Mendelson, *Chevron and Preemption*, 102 MICH. L. REV. 737, 783 (2004) (reporting that "only five" federalism impact statements had been filed "for the over 11,000 final rules" reviewed).

Much of the same may be said of courts. Although 28 U.S.C. § 2403(b) requires notice to a State's Attorney General whenever "the constitutionality of any statute of that State" affecting the public interest is drawn in question," providing the State with the litigation rights (far stronger protection than the administrative regime applicable, though

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that are responsible for oversight of the medical professions – and that have a strong and independent interest in ensuring that physicians are kept fully up-to-date about hazards associated with prescription drugs.

casually disobeyed, in *Wyeth*), this rarely, if ever occurs in implied preemption cases.

Finally, lax and casual standards for administrative agency conflict preemption create powerful incentives to bypass Congress entirely, particularly since in Congress – where States are represented – preemption proposals can be contested. Under our federal system, congressional debates over the appropriate role for state law should be the "main event," rather than a mere "tryout" prefatory to an agency preemption decision. *Wainwright v. Sykes*, 433 U.S. 72, 90 (1977). To paraphrase Justice Scalia, "only the most sporting of [industry interest groups]," would run the legislative gauntlet and seek preemption from Congress, if statutory silence plus an agency preamble (or brief), or a generalized claim of agency diversion, were enough to extinguish venerable common law rules nationwide. *See Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 548 (1992) (dissenting in part).

II. PETITIONERS' PROPOSED RULE OF BROAD IMMUNITY FOR GENERIC DRUG MANUFACTURERS FROM STATE LAW WOULD IMPAIR IMPORTANT STATE INTERESTS AND WOULD DISRUPT STATE HEALTH CARE AND CONSUMER PROTECTION POLICY

The immunity for manufacturers of generic drugs would have significant adverse consequences for the States as the principal protectors of their citizens' health, safety, and welfare; as guardians of the public fisc; and as licensors and regulators of their health care professionals. Petitioners' rule would create an odd disparity, invisible and unfathomable to ordinary consumers, between the legal remedies

respecting brand versus generic drugs. It would, in practical effect, make States financially responsible for injuries caused by the negligence of a class of for-profit corporations. It would give doctors and patients incentives not to select cost-saving generic substitutes. It would undermine basic premises of state legislation concerning substitution of generic drugs. While petitioners profess concerns about hypothetical burdens on the federal agency (going far beyond even those expressed by the agency), they entirely ignore the drastic implications their rule would have for the state-federal balance.

A. State Generic Substitution Laws Have Played an Important Role in the Development of Generic Drug Markets and Illustrate the States' Vital Interest in this Area

Partially in response to the enactment of Medicaid in 1965, and with the active encouragement of the FDA and the Federal Trade Commission (FTC), every State adopted laws permitting substitution of generic drugs between 1970 and 1984.[2] State

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[2] Many States drew guidance from the FDA's 1979 Model Drug Product Selection Act, which encouraged States to permit pharmacists to select cheaper generic drug equivalents for brand name prescriptions by requiring doctors to affirmatively indicate when substitution was not allowable. *See* 44 Fed. Reg. 2932 (1979); FTC, Bureau of Consumer Protection, Drug Product Selection (1979). Twenty-three States adopted or amended their generic drug substitution laws after the Model Act's promulgation. *See* Kenneth W. Shafermeyer, *et al.*, *The FDA Orange Book: Expectations Versus Realities*, 1 J. PHARM. & L. 13, 17 (1991). *See also, e.g.*, Nevada State Legislature, Background Paper 79-11, Generic v. Brand Name Drugs at 6 (1979).

"generic substitution" policies have also contributed significantly to the dramatic growth in the use of generic drugs.

All the States and the District of Columbia now have statutes providing for the substitution of generic drugs when a prescription refers to a brand drug.[3] These laws encourage, and often require, that pharmacists fill a prescription identifying a brand drug with a medically equivalent, lower-cost generic

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[3] ALA. CODE § 34-23-8; ALASKA STAT. § 08.80.295; ARIZ. REV. STAT. § 32-1963.01; ARK. CODE ANN. § 17-92-503; CAL. BUS. & PROF. CODE § 4073; COLO. REV. STAT. § 12-22-124; CONN. GEN. STAT. § 20-619; DEL. CODE ANN. tit. 24, § 2549; D.C. CODE § 48-803.02; FLA. STAT. § 465.025; GA. CODE ANN. § 26-4-81; HAW. REV. STAT. § 328-92; IDAHO ADMIN. CODE r. 27.01.01.188; 225 ILL. COMP. STAT. 85/25; IND. CODE § 16-42-22-8; IOWA CODE § 155A.32; KAN. STAT. ANN. § 65-1637; KY. REV. STAT. ANN. § 217.822; LA. ADMIN. CODE tit. 46, § 2511; ME. REV. STAT. ANN. tit. 32, § 13781; MD. CODE ANN., HEALTH OCC. § 12-504; MASS. GEN. LAWS ch. 112, § 12D; MICH. COMP. LAWS § 333.17755; MINN. STAT. § 151.21; MISS. CODE ANN. § 73-21-117; MO. REV. STAT. § 338.056; MONT. CODE ANN. § 37-7-505; NEV. REV. STAT. § 71-5403; NEV. REV. STAT. ANN. § 639.2583; N.H. REV. STAT. ANN. § 318:47-d; N.J. STAT. ANN. § 24:6E-7; N.M. STAT. § 26-3-3; N.Y. EDUC. LAW § 6816-a; N.C. GEN. STAT. § 90-85.28; N.D. CENT. CODE § 19-02.1-14.1; OHIO REV. CODE ANN. § 4729.38; OKLA. STAT. tit. 59, § 353.13; OR. REV. STAT. § 689.515; 35 PA. CONS. STAT. § 960.3; R.I. GEN. LAWS § 5-19.1-19; S.C. CODE ANN. § 39-24-30; S.D. CODIFIED LAWS § 36-11-46.1 -46.4; TENN. CODE ANN. § 53-10-205; 22 TEX. ADMIN. CODE § 309.3; UTAH CODE ANN. § 58-17b-605; VT. STAT. ANN. tit. 18, § 4605; VA. CODE ANN. § 54.1-3408.03; WASH. REV. CODE § 69.41.120; W. VA. CODE § 30-5-12b; WIS. ADM. CODE DHS § 107.10; WYO. STAT. § 33-24-149.

when one is available – unless the prescribing health professional has specifically directed that only the brand drug be used (often called a "Dispense as Written" instruction), or (in some jurisdictions) if the patient refuses substitution.[4] While state laws preserve physicians' discretion to specify that only brand drugs be dispensed, some require an express determination by the prescriber that the brand drug is "medically necessary,"[5] or forbid the pre-marking of prescription forms to preclude generic substitution, or require that "brand only" specifications be hand-written.[6]

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[4] For example, the Minnesota statute in respondent Mensing's case, *see* J.A. 402, provides that, if the doctor prescribes a brand drug and specifies "Dispense as Written," or "D.A.W.," the pharmacist shall dispense the specified brand drug, but that if the prescriber does not so specify, and "there is available in the pharmacist's stock a less expensive generically equivalent drug that, in the pharmacist's professional judgment, is safely interchangeable with the prescribed drug, then the pharmacist shall, after disclosing the substitution to the purchaser, dispense the generic drug, unless the purchaser objects." MINN. STAT. § 151.21(2), (3). *See also* LA. ADMIN. CODE tit. 46, § 2511 (statute at issue in *Demahy*).

[5] *E.g.*, TENN. CODE ANN. § 53-10-204(a)(1) (defining medical necessity as situations where "[a]n adverse reaction previously experienced by the patient to a generic equivalent" or a generic equivalent "has previously been demonstrated as ineffective for the patient"; or "[a]ny other clinically based prescriber determined need").

[6] *See, e.g.*, S.D. CODIFIED LAWS § 36-11-46.2; 22 TEX. ADMIN. CODE § 309.3(c)(2)(A),(C).

Recognizing that potential tort liability could affect physicians' willingness to allow generic substitution, or pharmacists' willingness to substitute generic for brand drugs even though authorized by the prescription, many States have enacted laws shielding health professionals from suits for substituting generic drugs in accordance with state law.[7]

The generic substitution statutes also attest to States' interest in ensuring that patients are aware of their options concerning generic substitution. Some States require that prescription forms make clear whether the physician has directed that only the brand drug be dispensed;[8] others require pharmacists to inform patients of lower-priced prescription options;[9] while still others require pharmacies to post prominent signs informing

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[7] *E.g.*, KAN. STAT. ANN. § 65-1637(c)(2) (physicians); N.Y. EDUC. LAW § 6816-a(6)(d); N.D. CENT. CODE § 19-02.1-14.1; 35 PA. CONS. STAT. § 960.6(B).''). *See also* ARIZ. REV. STAT. § 32-1963.01(G) (pharmacists); ALASKA STAT. § 08.80.295(b); MD. CODE ANN., HEALTH OCC. § 12-504(h).

[8] *E.g.*, WASH. REV. CODE § 69.41.120. ("[T]he prescription must be legible and the form shall have two signature lines at opposite ends on the bottom of the form. Under the line at the right side shall be clearly printed the words 'DISPENSE AS WRITTEN'. Under the line at the left side shall be clearly printed the words 'SUBSTITUTION PERMITTED'").

[9] *E.g.*, HAW. REV. STAT. § 328-92(a) (requiring that pharmacists, when filling a prescription for a brand drug, "offer the consumer an equivalent generic drug product" upon request, "inform the consumer of the savings," and "[i]nform the consumer of the consumer's right to refuse substitution").

customers of their option of filling their prescriptions with generic alternatives.[10]

State policies favoring generic substitution are given special force in the context of publicly-funded programs such as Medicare, Medicaid and State Children's Health Insurance (SCHIP). Some generic substitution statutes distinguish between governmentally financed health care programs and private insurance or self-funding patients. *See, e.g.*, IND. CODE §§ 16-42-22-8, 16-42-22-10. Many States require that prescriptions for patients whose drug expenses are covered by those programs be filled with generic drugs.[11] The Federal government has

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[10] For example, Connecticut requires each pharmacy to post, on a sign bearing large block letters posted at the prescription counter, "THIS PHARMACY MAY BE ABLE TO SUBSTITUTE A LESS EXPENSIVE DRUG PRODUCT WHICH IS THERAPEUTICALLY EQUIVALENT TO THE ONE PRESCRIBED BY YOUR DOCTOR UNLESS YOU DO NOT APPROVE." CONN. GEN. STAT. § 20-619 (d). *See also* FLA. STAT. § 465.025 (7); IDAHO ADMIN. CODE r. 27.01.01.188; OR. REV. STAT. § 689.515.

[11] "Since 2000, there has been a steady trend toward increased mandatory generic substitution. In 2005, nearly all states * * * reported that they require generics to be dispensed when available." Henry J. Kaiser Family Foundation, State Medicaid Outpatient Prescription Drug Policies: Findings from a National Survey (October 2005). *See also* William H. Shrank, *et al.*, *State Generic Substitution Laws Can Lower Drug Outlays Under Medicaid*, 29 HEALTH AFF. 1383, 1384 (2010) (discussing varieties of mandatory generic substitution and patient consent laws affecting state Medicaid programs); *id.* at 1386 Ex. 1 (table).

actively encouraged these policies. *See, e.g.*, 42 U.S.C. § 1396b(z)(2)(E); Office of Inspector General, Department of Health and Human Services (HHS), Generic Drug Utilization in State Medicaid Programs at i (2006) ("The [HHS] Centers for Medicare & Medicaid Services (CMS) has encouraged generic drug substitution * * * as a safe and effective way for States to increase generic drug utilization and reduce costs.").

B. Petitioners' Proposed Tort Immunity for Generic Manufactures Would Seriously Unsettle State Policy

The broad tort immunity sought here would have far-reaching and problematic consequences for the laws just summarized, and the important state interests and policies these serve. States have encouraged the substitution of generic drugs because of the significant benefits these drugs' lower costs offer for state citizens, and for state-funded public health and insurance programs. They have proceeded on the premise that (save for unusual instances of individual medical need), generic drugs are not, from citizens' perspective, materially different from brand ones, except for the lower price.

Granting the federal law tort immunity petitioners seek would mean that, contrary to appearances, there is, in fact, a significant – but latent – difference between every brand and every generic drug from the perspective of doctor and patient. If a consumer is injured as a result of an inadequate warning on a brand drug, he would have recourse under state law against the manufacturer. But if the injury was caused by "*the same*" warning on a bioequivalent generic drug, the injured person

has no remedy against a manufacturer who knew of the danger but did nothing to prevent it.

Such a regime is not only "bizarre" from the perspective of the unwitting consumer, *see Demahy*, 593 F.3d at 449, but it would present serious problems for States. The state generic substitution laws just discussed – which have been enacted with the active encouragement of the federal government (and without objection from generic drug manufacturers) – have informed citizens that they should not hesitate to accept generic alternatives, even when their doctor has prescribed the brand drug. Often, particularly in the case of poorer citizens under programs like Medicaid, these policies provide that they *must* accept the generic alternative. Similarly, the statutes have encouraged or required physicians to allow generic substitution unless there is a *medical* reason for specifying the brand, and, in many circumstances, have mandated that pharmacists fill prescriptions for brand drugs with generic substitutes.

Petitioners' preemption rule would undermine basic premises of this regime. Consumers without medical or pharmacy degrees would be unlikely to be aware of this major disparity between the legal incidents flowing from the choice between brand and generic drugs. Out of candor to their citizens, States might well alter their rules, to inform the public of that potentially significant disparity between products they have been repeatedly told are "the same." And disseminating the message that "MANUFACTURERS OF GENERIC DRUGS CANNOT BE LIABLE FOR FAILURE TO WARN OF HEALTH RISKS ASSOCIATED WITH THEIR PRODUCTS" could lead some patients – at least

those financially able to do so – to spurn generic drugs, undermining the policies of the Hatch-Waxman Act and state generic substitution laws alike.

Immunity for manufacturers would also have significant repercussions for States in their capacity as regulators of the health care professions. State laws shielding physicians and pharmacists from liability for allowing or undertaking generic substitution reflect the commonsense reality that legal liability rules can influence the behavior even of highly trained professionals concerning the choice between medically equivalent drugs. If generic drug manufacturers are immune, however, some doctors may be deterred from allowing generic substitution, knowing that they alone could face liability if a generic drug caused their patient to suffer injury. If they specified the brand name drug, however, the situation would be markedly different. Even doctors who did not share that concern or chose not to act on it might feel qualms about relegating their patient – at least without express consent – to a drug whose manufacturer would be immune from suit when it failed to disclose information that would have prevented grievous harm. (Whether such action would be permissible under current laws limiting brand specification to "medical necessity" is unclear.) And, of course, physicians' very ability to treat their patients effectively depends upon their receiving up-to-date and comprehensive information concerning health risks associated with drugs.

Indeed, this calls attention to two very basic embarrassments in petitioners' argument. First, while their plea for preemption depends almost entirely on the notion that Congress or the FDA

require "sameness" for generic and name-brand drugs, these arguments are made in service of a rule of permanent *difference*. Second, the more modest purposes that "sameness" actually serves in the regime – structuring the *process* by which manufacturers make required label changes to warn properly against newly known risks, to avoid unnecessary consumer confusion – would be particularly undermined. Whatever individual regulators or physicians or insurers decided, the clear, coherent, and largely uniform message concerning substitution would be compromised.

A rule by which generic drug manufacturers can remain silent despite knowledge of serious risks would impair States' vital interest in promoting the health and safety of their citizens, *see Wyeth*, 129 S. Ct. at 1202-03 ("State tort suits uncover unknown drug hazards and provide incentives for drug manufacturers to disclose safety risks promptly"); *cf. Bruesewitz v. Wyeth LLC*, No. 09-152, 2011 WL 588789 (U.S. Feb. 22, 2011) ("Design-defect torts, broadly speaking, have two beneficial effects: (1) prompting the development of improved designs, and (2) providing compensation for inflicted injuries.").

Immunizing generic drug manufacturers would not only deprive injured citizens of compensation, but would leave others, often state governments, financially responsible for their care. "[S]tates' traditional authority to provide tort remedies to their citizens," *Silkwood v. Kerr-McGee Corp.*, 464 U.S. 238, 248 (1984), exists not only because the political community's moral concern for its members' welfare and interest in compensation, but also because, when a person becomes injured or severely disabled, the State will often bear many of the costs

of providing medical care, rehabilitation, and family support services.

The immunity petitioners claim simply was not part of the legal background against which States adopted their prescription drug laws, including the generic substitution statutes that played such a critical role in promoting the generic drug industry. Had Congress – in 1984, or at any point since – actually proposed to preempt state tort remedies against manufacturers of generic drugs, States would have had the opportunity to present their objections through their political representatives in Congress, "the principal means chosen by the framers to ensure the role of the States in the federal system." *Garcia*, 469 U.S. at 550, 551 n.11 (citing, *inter alia*, Herbert Wechsler, *The Political Safeguards of Federalism: The Role of the States in the Composition and Selection of the National Government*, 54 COLUM. L. REV. 543 (1954)).[12]

III. PETITIONERS' OBSTACLE PREEMPTION ARGUMENTS FAIL

As an alternative to their conflict "impossibility" arguments, Petitioners Pliva, *et al.* and their amici seek to enlist this Court's "implied[] preempt[ion]" decision in *Buckman*, 531 U.S. at 347, insisting that reversal here follows from the holding or reasoning of that case and others, such as *Arkansas Louisiana Gas Co. v. Hall*, 453 U.S. 571 (1981)

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[12] As the statutory regime in *Bruesewitz* illustrates, on those rare occasions where Congress decides, in the face of truly compelling policy concerns, to preempt traditional State tort law, it typically acts with a scalpel, not a chain saw.

(*ArkLa*), claimed to rest on the same "principle." But these arguments reflect an extravagant misreading of these decisions. Petitioners' reading violates first principles of this Court's preemption jurisprudence, and would allow the casual, unconsidered overriding of settled state policies in a host of areas, with consequences as disruptive as those we have just summarized.

A. *Buckman* Does Not Support Preemption Here.

To begin, contrary to the impression fostered by petitioner's brief, *Buckman* is hardly a milestone in this Court's federalism and preemption jurisprudence. It has appeared in a majority opinion only once, when the Court in *Wyeth* observed that the "dissent's reliance [on it was] * * * especially curious," as *Buckman* had "involved state-law fraud-on-the-agency claims," and had expressly distinguished tort suits involving "health and safety," 129 S. Ct. at 1231 n.3. The Court in *Buckman* rebuffed a decidedly non-traditional tort cause of action, ostensibly pleaded under Pennsylvania common law, whereunder a person injured by an FDA-approved medical device could recover from a contractor involved in securing federal approval by showing that the consultant had deceived the agency. In holding that cause of action preempted, *Buckman* emphasized that ordinary preemption principles were inoperative, because, unlike claims in cases like *Medronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996), and *Silkwood* "based on traditional state tort law principles" and implicating "federalism concerns and the historic primacy of state regulation of matters of health and safety," 531 U.S. at 342, "[p]olicing fraud against federal agencies is hardly 'a field which the States have traditionally

occupied,'" *id.* at 347 (quoting *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218, 230 (1947)). And whereas the duties sued upon in the earlier cases were independent of federal statutes, the novel cause of action in *Buckman* owed "its existence" to the FDCA. 531 U.S. at 353.

Not only would the "very subject matter" of the claim in *Buckman* be defendants' "relationship" and compliance with requirements governing regulated parties' "dealings with" the agency – which the Court observed were "inherently federal in character" – but a judgment for plaintiffs would have effectively impugned the validity of the FDA approval decision, *see* 531 U.S. at 347 (describing allegation that "improperly given market clearance" led to injury).

Buckman contrasted "clear evidence * * * that Congress intended [these statutory duties to] be enforced exclusively by the Federal Government" with *Silkwood*, in which Congress had disclaimed interest in displacing "adequate remedies for those injured." 464 U.S. at 257. The *Buckman* Court noted that the tort would intrude on the agency's authority to determine and calibrate its own response to misconduct directed toward it by a regulated party, and did so unnecessarily, given the manifold ways the "federal statutory scheme amply empowers FDA to punish and deter fraud against the Administration," 531 U.S. at 348.

To summarize the *Buckman* decision is to appreciate why the case does not support the preemption claim here. Unlike the exotic theory of recovery there, the duties on which the plaintiffs' claims are based are ones traditionally imposed under state common law. *See* 531 U.S. at 352 ("'Silkwood's claim was not based on any sort of

fraud-on-the-agency theory, but on traditional state tort law principles of the duty of care").[13] Accord *Wyeth*, 129 S. Ct. at 1195 n.3. Respondents' claims here do not "exist solely by virtue" of federal requirements, *Buckman*, 531 U.S. at 353 (distinguishing *Lohr*, 518 U.S. at 481), and the gravamen of those claims is not to "police" the "relationship" between federal agencies and regulated entities. Instead, respondents seek only compensation for a breach of traditional common law safety duties running from the manufacturer of a product to an injured consumer. Federal law, and the federal agency, enter the picture not because they are the font (let alone the sole source) of the plaintiffs' claim, but because the defendant has asserted that a verdict could be inconsistent with federal obligations. And there is no claim here that these suits impinge on the FDA's discretion in responding to misconduct in regulated entities' "dealings with" the agency. See Holmes v. *Sec. Investor Prot. Corp.*, 503 U.S. 258, 269-70 (1992) ("[D]irectly injured victims can generally be counted on to vindicate the law * * * without any of the

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[13] Indeed, at oral argument in *Buckman*, the United States, which took an aggressively pro-preemption position, acknowledged that traditional common law claims were not preempted: "The fraud claim is preempted, but if there is negligent design, negligent manufacturing, *failure to warn*, common law malpractice, all of those claims *are available*, but insofar as they would be asserting an essential element of the claim would be that the FDA was defrauded, that is an area of exclusive federal concern, and the State common law cause of action would be preempted." No. 98-1768, Tr. at 21 (emphasis added).

problems attendant upon suits by plaintiffs injured more remotely."). To the contrary, federal law provides that a generic drug is misbranded if the label lacks adequate warnings of a serious risk for which there is reasonable evidence of an association *See* 21 U.S.C. § 352(f)(2), 21 C.F.R. § 201.57(e). If presented with a recommendation to cure an existing situation of misbranding, the FDA would surely act.

Perhaps most fundamentally, the claims here, unlike those in *Buckman* and *ArkLa*, do not entail any sort of collateral attack on an agency action or decision. Here, the plaintiffs do not complain that the FDA's approval of the NDA for Reglan, or of ANDAs for metoclopramine, were invalid or harmful or the cause of their injuries. *See Buckman*, 531 U.S. at 347 (claim that "improperly given market clearance" led to injury); *Altria Group, Inc. v. Good*, 129 S. Ct. 538, 549 (2008) (explaining that claims held preempted in *Riegel v. Medronic, Inc.*, 552 U.S. 312, 336-37 (2008), had "sought to impose different requirements on precisely those aspects of the device that the FDA had approved"); *Williamson v. Mazda Motor of Am., Inc.*, No. 08-1314, 2011 U.S. Lexis 1711 at *16-*22 (distinguishing *Geier v. Am. Honda Motor Co.*, 529 U.S. 861 (2000)).

Respondents here claim that defendants' adherence to a label that failed to warn of risks that became known post-marketing was irresponsible and harmful, in violation of duties state law (as well as the FDCA) has long imposed. The FDA denies that its approval of respondents' drugs (or labels) may be treated as its judgment of adequacy for all times. Indeed, *Wyeth* settles that responsibility for the label (and for adequate warnings) is the manufacturer's, not the agency's, and that the federal labeling

obligation (like the state warning duties) depend on the hazards *currently* known, not those at the time of the agency's NDA or ANDA decisions. *See* 129 S. Ct at 1197-98.

These fundamental differences also explain why *ArkLa* and *Kalo Brick* lend no support for preemption here. Both those decisions arose from state court suits that sought to attack decisions of federal agencies on matters over which Congress had given the agencies "exclusive and plenary" authority. *Kalo Brick*, 450 U.S. at 321. In *Kalo Brick*, a shipper sought to recover under Iowa law for damages resulting from an interstate railroad's decision to abandon track – action the Interstate Commerce Commission specifically considered and approved. In holding the suit preempted, the Court emphasized that the "exclusive and plenary nature of the Commission's authority to rule on carriers' decisions to abandon lines [was] critical" to a congressional scheme developed after "'[m]ultiple control' ha[d] proved 'detrimental to the public interest,'" describing the suit as "little more than an attempt by a disappointed shipper to gain from the Iowa courts the relief it was denied by the Commission." *Id.* at 320, 324. Even under these circumstances, the Court took care to assure itself that preemption would "not leave a shipper in respondent's position without a remedy if it is truly harmed." *Id.* at 331.

ArkLa applied an even more venerable rule of plenary federal agency jurisdiction: the "filed rate doctrine," which forbids parties subject to administrative rate regulation, such as the natural gas producer in *ArkLa* (which was regulated by the Federal Power Commission) from collecting rates

other than the one "filed" and approved by the agency. 453 U.S. at 573.

Although the FDA regime here and the one in *ArkLa* may bear a superficial similarity – the FPC approved Hall's rate, and FDA approved petitioners' labels – they are actually in relevant respects polar opposites: The premise of the "filed rate doctrine" (and the holding of *ArkLa*) is that a final agency judgment of reasonableness may not be revisited (even by the agency itself); in contrast, it is a *violation* of the federal statute here (as well as of the common law) to continue to give agency-"approved" warnings once the manufacturer possesses drug risk information showing they are inadequate, *see* 21 C.F.R. § 201.57(e).

The premises of and purposes served by the unusually stringent rate doctrine are also strikingly different: strict enforcement of publicly-filed rates is essential to combating a primary "evil" against which those laws are directed – price discrimination, collecting differing rates from similarly-situated customers. And the stringency of the doctrine works against *regulated* parties, like the gas seller in *ArkLa*, holding them to arrangements *they made* and represented to the agency were "reasonable" (but did not turn out well) *until they file and obtain agency approval for more favorable ones*. Those disadvantaged by inadequate drug labels, in contrast, are blameless members of the general public, whose bodily injuries could have been prevented through due care.

While a filed-rate regime gives those regulated strong incentive to file and seek approval of higher rates as soon as they become aware of changed circumstances that would make those "reasonable,"

the incentives here, as *Wyeth* recognized, are wholly different: Labels (accurately) warning consumers and physicians that products are more dangerous than currently represented – and may safely be used only for weeks instead of months – are not in regulated parties' commercial interest. A regime that allowed generic manufacturers a complete defense based on the inaction of a brand-name maker, even when the generic company is well aware of the deficiency (and even when, as with some 32% of drugs, the brand-name company has simply left the field, *see* Resp. Br. at 20 & n.24) is even further from the core safety purposes of the statute. Of course, the "harshness" of finality rules of the sort in *ArkLa*, which hold regulated parties to the *economic* consequences of their own decisions, is not readily compared to that of a regime that would lead to unnecessary, irreversible physical harm for members of the public the safety regime is meant to protect. *See Burnet v. Cornado Gas Co.*, 285 U.S. 393, 406 (1932) (Brandeis, J., dissenting) (in economic regulation, it is more important that a matter be "settled than that it be settled right").

This case would be closer to *ArkLa* if, instead of relying on FDA's initial approval of their ANDA (subject to modification as new risk information emerged), petitioners were seeking preclusion based on an *actual* agency decision – *e.g.*, a ruling against a citizen petition by generic manufacturers seeking approval of warnings reflecting the later-developed information suggesting that the risk of tardive dyskinesia had been significantly understated and that prolonged use is more dangerous than first recognized. But that is not what happened. Here there is no such agency decision to impugn; and no

claim that petitioners did other than sit on their hands.

To be sure, petitioners' efforts to more accurately warn the public *could* ultimately meet with FDA disapproval. Like the manufacturer's argument in *Wyeth*, however, that argument confuses the statute's *primary* requirements and objectives – adoption of currently adequate safety warnings by *all* manufacturers – with the particular procedures the agency has adopted for accomplishing them, in an orderly fashion to prevent undue confusion. And as in *Wyeth*, there is no reason here to assume (let alone any evidentiary basis for concluding) that the agency would have stood in petitioners way. *Cf. Rice v. Norman Williams Co.*, 458 U.S. 654, 659 (1982) ("The existence of a hypothetical or potential conflict is insufficient to warrant * * * pre-emption"). Indeed, in this case, the FDA, eventually ordered a new, "black box" label for this drug.

These cases do not ask a state court (or federal courts applying state law) to overturn or impeach *any* FDA decision. Moreover, Congress did not provide that the FDCA is an "exclusive form of regulation" for drug warnings. As *Wyeth* affirms, this is an area in which state and federal law have coexisted for generations, and federal law has never attempted to install federal remedies for persons injured as a result of defective warnings.

B. Petitioners' Efforts to Invent Sweeping New Implied Conflict Preemption Doctrines Based upon Language from *Buckman* Should Be Rejected

Rather than acknowledge differences that are fundamental, petitioners and *amici* seek to extract

language in *Buckman*, *ArkLa* and *Kalo Brick* from the context in which it appears. They attempt to derive a set of preemption "principles" strong enough to be availing here, arguing that any tort claim that entails consideration of an agency decision to act or not to act is preempted. They extend this argument to any decision that has the potential to incidentally result in "additional burdens" on an agency or its personnel, Pliva Br. at 30 (quoting *Buckman*, 531 U.S. at 351) – or "interfere" with what could be considered an agency decision not to act – is preempted. But the "rules" they identify are contrary in multiple central respects to controlling precedent, and ignore basics of the relationship between federal and state law.

First, what petitioners would deride as "speculation," Pliva Br. 48-49 – considering what would have happened – is no incident of an exotic tort cause of action; it is a feature inherent in common law litigation (indeed, virtually all litigation). Their suggestion that *Buckman*, *Arkla*, and *Kalo* rest on a categorical rule against any state law consideration of federal agency activities simply wishes away the critical common feature of those cases. All involved collaterally attacking an agency's decision on a matter within its exclusive, plenary jurisdiction.[14] Indeed, the expansive reading of

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[14] While the attack in *Buckman* was not presented as an attack on the substance of the *agency's* decisionmaking, the claim concerned a subject – responding to fraud – no less within the aggrieved agency's primary jurisdiction, *see* 531 U.S. at 349 n.3, and the judgment sought would have necessarily implied the invalidity of the agency's action approving the device.

those cases cannot survive *Wyeth*, where preemption was rejected though the plaintiff's ultimate ability to recover in tort (the same tort as here) depended on essentially the same issue raised here: whether the agency *would have* approved a label with warnings that accurately reflected currently known risks. The fact that this question could or would enter a court's analysis did not warrant preemption there, and it does not make federal regulation a "critical element" in the sense meant by *Buckman*. As noted, *Buckman* involved duties running to the agency and the entire cause of action owed its existence to federal law.

Petitioners' only response – the only one possible – is that brand-name manufacturers may provisionally change labels pending FDA approval, whereas (they say) generic manufacturers must obtain approval first,– meaning that the question arises as part of plaintiffs' case in chief and is therefore an "element." Pliva Br. 50-54. But this is untenable for several reasons.

At the outset, it would be a strange rule of *obstacle* preemption that distinguished between two causes of action that entail courts' undertaking the same inquiry – whether the federal agency would have approved a safer label. And the extent to which the statute or agency regulations constrain generic manufacturers' powers to take "unilateral" (temporary) action to give warnings is itself a disputed question. (Though the agency advances a somewhat narrower understanding of powers retained by generic manufacturers than do respondents, it does so in the context of expressly disclaiming preemptive effect or intent for its interpretation).

But even if petitioners' account were accepted, it only highlights internal tensions basic to their position. It simultaneously emphasizes the formal distinction between the "elements" of a cause of action (as against defenses) while at the same time denying any significance to the contours of the actual state laws (of Louisiana and Minnesota) under which respondents sued. Indeed, it would presumably be within the state law's ken to allow plaintiffs to carry any proof burden by relying on a presumption, stated in *Wyeth* and grounded in experience as well as statutory text, that the FDA would not have disapproved more accurate and effective warnings. *See* 21 U.S.C. § 352(f)(2), 21 C.F.R. § 201.57(e).

Federal courts – even this Court – are not authoritative expositors of state law, and it would be surprising for categorical preemption rules to depend on federal determination of what qualifies as an "element" for pleading a state tort cause of action. Neither federal action nor "exclusively" federal law plays a role remotely like in *Buckman*, where plaintiffs were third parties seeking to enforce particular duties owed only to the federal agency in the context of a prior presumptively-valid agency decision. The Court recognized that explicitly, explaining that some, but not every, federal law duties can be sued upon – distinguishing between regulations that parallel common law duties to the public and those running to the agency. 531 U.S. at 353.

Worse still for petitioners, their logically (if not legally) conceivable basis for distinguishing this case from *Wyeth* is fatally inconsistent with their reliance on the position taken by the United States in

Warner-Lambert Co. v. Kent, 552 U.S. 440 (2008) (per curiam affirmance by equally divided Court). In that case, one primary argument *against* preemption was that the issue of fraud on the agency only arose in the course of overcoming a defense, *see Louisville & N.R. Co. v. Mottley*, 211 U.S. 149, 153 (1908), and the government as amicus argued that the compliance defense would be readily made out in every case – so the real issue in cases under the Michigan law would be the same as in *Buckman*. *See* U.S. *Kent* Amicus Br. at 31 (asserting that distinction between "'element' and . . . 'affirmative defense' [is] "immaterial" and that "no reason" why "label would matter" under *Buckman*); *cf. Grable & Sons Metal Prods., Inc. v. Darue Eng'g & Mfg.*, 545 U.S. 308, 320 (2005) (allowing federal jurisdiction over state-law claim with "dispositive and contested federal issue at [its] heart").

Of course, the arguments pressed in that brief are of no more legal or precedential significance than those the same agency advanced – without success – in *Wyeth*; indeed, there was a substantial overlap between the two. *See* U.S. *Wyeth* Amicus Br. 25-26, and the Executive Branch has since taken a materially different view of these questions, *see* Memorandum on Preemption, 2009 Daily Comp. Pres. Doc. 384, at 1 (May 20, 2009); *Riegel*, 552 U.S. at 327 ("The agency's earlier position *** is even more compromised, indeed deprived of all claim to deference, by the fact that it is no longer the agency's position.").

But accepting the Solicitor General's position in *Kent* would not entitle petitioners to prevail here. In that case, the government argued that, notwithstanding the source of the duty enforced, the

express focus on fraud against the FDA interfered with the "'inherently federal'" relationship between the agency and regulated parties, so that, under *Buckman*, the presumption against preemption did not apply. U.S. *Kent* Amicus Br. at 15. Here, by contrast, respondents' state-law claims do not require them to prove the FDA was defrauded; the focus is on whether the defendant had information about serious health risks associated with its product. The state law theory does not require a court to revisit and scrutinize a past agency decision and declare it tainted. And the claim here, unquestionably, is subject to the presumption against preemption.

Petitioners' other arguments depend on taking statements the *Buckman* opinion offered in support of its limited, unexceptionable holding as the building blocks for a preemption regime entirely unencumbered by principles settled in controlling decisions of this Court, including recent and unanimous ones. Of course, assertions that leaving state law claims unpreempted would "impose" costs or exert "extraneous pull" (Pliva Br. 61) (quoting *Buckman*, 531 U.S. at 353), entail tightly circular reasoning: the "pull" of state tort liability is "extraneous" only if Congress's had in fact intended a "scheme" of field preemption. *Compare Wyeth*, 129 S. Ct. at 1202 (describing "state law as a complementary form of drug regulation"); *see generally Gade*, 505 U.S. at 110 (Kennedy, J., concurring) (argument that "assumes that Congress intended exclusive federal jurisdiction" is "not an application of our pre-emption standards *** but a conclusory statement of pre-emption").

And the unanimous decision in *Williamson*, refusing preemptive effect to an agency *decision* not to impose a requirement, definitively inters the notion that *every* instance of agency inaction may be treated as a "delicate balance" that state law may not "skew." *See Williamson v. Mazda Motor of Am., Inc.*, No. 08-1314, 2011 U.S. Lexis 1711 at *20 (U.S. Feb. 23, 2011) (to "infer from the mere existence of [agency] cost-effectiveness judgment" a bar to state law would impermissibly "treat all such federal standards as if they were maximum[s]"). *See also Altria Group*, 129 S. Ct. at 551 n.14 (refusing to rely on agency inaction to support preemption claim "when that inaction is in part the result of the [defendant's] failure to disclose study results").

As for claims of burdens on agency decisionmaking or personnel, these are surely self-serving and doubtful on their own terms. It cannot be the law that any development in state law that might have the effect of encouraging prospective defendants to provide more information to or seek more discovery from federal agencies – a factor that certainly could arise in many a products liability, environmental, or state consumer protection case, among others – serves as a basis for deeming such state claims *preempted*. *See, e.g., Bates v. Dow Agrosciences LLC*, 544 U.S. 431, 443 (2005) ("quite wrong" to treat changes a verdict might "'induce'" as a "requirement"). Even when pressed by federal officials, such assertions do not merit – or receive – uncritical acceptance: "mere 'administrative convenience,'" *Frontiero* v. *Richardson*, 411 U.S. 677, 688 (1973), is not a transcendent constitutional value, and in *Clinton v. Jones*, 520 U.S. 681 (1997), the Court resisted claimed distraction as a basis for a discretionary postponement of a trial against the

President of the United States, declining to credit a "predictive judgment" of "a deluge of * * * litigation," noting that other "[s]itting Presidents have responded to court orders to provide testimony and other information." *Id.* at 704. *See also Gonzales v. O Centro Espirita Beneficente U.D.V.*, 546 U.S. 418, 435-36 (2006) ("The Government's argument echoes the classic rejoinder of bureaucrats throughout history": If I make an exception for you, I'll have to make one for everybody, so no exceptions").

The arguments from deluge and distraction here are stranger still. First, the federal agency that petitioners claim to protect does not agree that any kind of broad preemption is required on that basis. Moreover, the "information deluge" they warn against is not so much a prediction as a threat. In practice, the premise that more information is a good thing, *see Thompson v. Western States Med. Ctr.*, 535 U.S. 337, 375 (2002), applies when the subject matter is late-emerging information concerning serious safety hazards of consumer products. If petitioners and others did in fact flood the agency with useless information, there is every reason to assume the FDA has ample tools at its disposal, short of nationwide preemption of state law remedies for injured parties, to manage the quantum of what is submitted.

Indeed, the notion that a potentially increased inflow of "unwanted" information or incidental distraction of federal agency personnel could be a serious argument in favor of displacing a vast swath of traditional state law and policy is an index of how far petitioners' claims stray from the core principles of federalism undergirding this Court's preemption doctrine – and of how important it is to guard

against expansive, causal claims of "implied preemption."

Conclusion

The judgments of the courts of appeals should be affirmed.

Respectfully submitted,

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AMICUS CURIAE BRIEF

11

Nos. 09-993, 09-1039, and 09-1501

IN THE

Supreme Court of the United States

PLIVA, INC., ET AL., *Petitioners*,

v.

GLADYS MENSING, *Respondent*.

ACTAVIS ELIZABETH L.L.C., *Petitioner*,

v.

GLADYS MENSING, *Respondent*.

ACTAVIS, INC., *Petitioner*,

v.

JULIE DEMAHY, *Respondent*.

On Writs of Certiorari to the United States Courts of Appeals for the Fifth and Eighth Circuits

BRIEF OF PUBLIC CITIZEN AND AARP AS *AMICI CURIAE* IN SUPPORT OF RESPONDENTS

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INTEREST OF *AMICI CURIAE*[1]

Amici curiae Public Citizen and AARP are national non-profit organizations that represent the interests of consumers, including many who regularly use generic prescription drugs. Public Citizen is a membership organization devoted to research, advocacy, and education on a wide range of public-health and consumer-safety issues, including safe, effective, and affordable health care. Since its founding in 1971, Public Citizen has assessed the safety and efficacy of drugs, provided information on drug safety to the public, and petitioned the Food and Drug Administration (FDA) to act to reduce safety risks. Public Citizen has a longstanding interest in fighting exaggerated claims of federal preemption of state health and safety laws, and its lawyers have represented parties in many significant federal preemption cases, including *Warner-Lambert Co., LLC v. Kent*, 552 U.S. 440 (2008) (Mem.), *Riegel v. Medtronic, Inc.*, 552 U.S. 312 (2008), and *Medtronic, Inc. v. Lohr*, 518 U.S. 470 (1996).

AARP, an organization for persons 50 years old and over, works to foster the health and economic security of people as they age. To that end, AARP supports efforts at state and national levels to ensure access to safe and effective health care services and products. AARP is concerned about the safety of prescription drugs because older people disproportionately use them. AARP supports

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[1]No counsel for a party authored this brief in whole or in part, and no counsel for a party or party made a monetary contribution intended to fund the preparation or submission of this brief. No person or entity other than *amici curiae* made any monetary contribution to this brief's preparation or submission. The parties' letters of consent to the filing of amicus briefs have been filed with the Clerk.

laws and public policies that protect its members' rights and preserve the availability of legal redress when its members are harmed in the marketplace.

Amici are filing this brief because this case has the potential to broadly impact the safety of prescription drugs. As this Court noted in *Wyeth v. Levine*, 129 S. Ct. 1187, 1202 (2009), "[s]tate tort suits uncover unknown drug hazards and provide incentives for drug manufacturers to disclose safety risks promptly." They also "serve a distinct compensatory function that may motivate injured persons to come forward with information." *Id.* Generic drugs account for approximately 70 percent of prescriptions filled in the United States. Barring failure-to-warn claims against generic drug manufacturers would decrease the companies' incentive to disclose safety risks promptly, reduce injured consumers' motivation to come forward with information, and deny consumers redress for the injuries they suffer when the drugs they take lack appropriate warnings.

Amici recognize that generic drugs are important in providing affordable drugs to consumers, including the elderly. Indeed, because of the benefits to consumers of having access to generic drugs, representatives of both Public Citizen and AARP testified in support of abbreviated procedures for approval of generic drugs during hearings on the Hatch-Waxman Act when it was being considered by Congress. As AARP testified: "We think that this little bill has the potential for being the biggest consumer interest piece of legislation in this decade." *Drug Legislation: Hearings on H.R. 1554 and H.R. 8605 Before the Subcomm. on Health and the Env't of the House Comm. on Energy and Commerce*, 98th Cong.

59 (July 25, 1983). *Amici* are concerned, however, that, through preemption, a statute intended to provide consumers with increased access to *safe* generic drugs will be used to deny consumers necessary protections against *unsafe* ones.

SUMMARY OF ARGUMENT

State-law failure-to-warn claims further the purposes of the Hatch-Waxman Act. In enacting Hatch-Waxman, Congress sought to make generic drugs available to American consumers, but not at the expense of drug safety. The goal was safe, affordable drugs. State-law claims against generic drug manufacturers create incentives for those companies to ensure that their drugs are safe and contain appropriate warnings, and they provide relief to consumers who are injured by generic drug companies' failure to meet their duties of care. In contrast, holding state-law claims against generic drug manufacturers preempted would effectively punish consumers for choosing generic drugs over their name-brand alternatives. And it would send the message that generic drugs are less trustworthy than name-brand drugs—contrary to Congress's goal of reducing drug prices through competition by generic drugs.

That generic drugs do not enter the market until after the patent on the name-brand drug has expired, and therefore not until years after the name-brand drug has been on the market, does not eliminate the need for generic drug manufacturers to be alert to evidence of undisclosed risks and the need for additional warnings. Whether or not drugs are safe and what sorts of warnings are necessary are often not known until drugs have been

on the market for years. Particularly because generic drugs have a large share of the market, it is important that generic drug manufacturers have incentives to promptly and appropriately disclose safety risks.

The extent to which generic drug manufacturers have authority to alter their labels is disputed by the parties here. But it is uncontested that, at the least, they are free to propose new warnings to the Food and Drug Administration (FDA) and to ask the FDA to send "Dear Doctor" letters alerting health-care professionals to newly discovered risks. Because generic drug manufacturers can take measures to ensure that their products have adequate warnings—measures not only permitted but encouraged by the federal regulatory scheme—state-law failure-to-warn claims are not preempted.

ARGUMENT

I. The Hatch-Waxman Act Does Not Sacrifice Safety to Competition.

State-law claims against generic drug companies for failure to fulfill their duty to warn consumers of their products' risks are consistent with the goals of the Hatch-Waxman Act. *See Drug Price Competition and Patent Term Restoration Act*, Pub. L. No. 98-417, 98 Stat. 1585 (1984). Congress passed Hatch-Waxman in 1984 to make low-cost generic drugs more available to the public. *See* H.R. Rep. No. 98-857, pt. 1, at 14 (1984). It estimated that approximately 150 off-patent drugs first approved after 1962 had no generic equivalents and that making generic versions more easily available "would save American consumers $920 million over the [following] 12 years." *Id.* at 17.

Congress sought to achieve the goal of making low-cost drugs available to the public by reducing generic drug companies' barriers to enter the market. To this end, and out of recognition that generic drug companies need not duplicate previously conducted tests to demonstrate that their drugs are safe and effective enough to be approved, the Hatch-Waxman Act releases generic drug manufacturers from the obligation to submit the clinical study results needed to support a new drug application (NDA). Instead, a generic drug manufacturer may submit an abbreviated new drug application (ANDA) containing information showing that the generic drug's conditions of use, active ingredients, route of administration, dosage form, labeling, and strength are the same as those of the corresponding name-brand drug, and that the generic is bioequivalent to the name-brand drug. Pub. L. No. 98-417, § 101, *codified at* 21 U.S.C. § 355(j)(2)(A)(i)-(v).

Although, Hatch-Waxman sought to quickly "make available more low cost generic drugs," H.R. Rep. No. 98-857, pt. 1, at 14, it did not pursue that aim at all costs. In particular, Congress did not abandon the requirement that drugs be safe. "There is no indication that when Congress passed the Hatch-Waxman Amendments it intended the goal of delivering low cost generic drugs to supplant the FDCA's overall goal of providing consumers with safe and effective drugs." *Gaeta v. Perrigo Pharms. Co.*, __ F.3d __, 2011 WL 198420, at *11 (9th Cir. Jan. 24, 2011). Rather, the policy objective was to "get[] *safe and effective* generic substitutes on the market as quickly as possible." H.R. Rep. No. 98-857, pt. 2, at 9 (emphasis added). Indeed, the law's provisions demonstrate a continued focus on maintaining drug safety and

effectiveness. *See, e.g.*, Pub. L. No. 98-417, § 101, *codified at* 21 U.S.C. § 355(j)(2)(C)(ii) (providing that the Secretary can deny a petition to file an ANDA for a generic drug with a different active ingredient than an approved drug if the drug "may not be adequately evaluated for approval as safe and effective on the basis of the information required to be submitted" in the ANDA). In short, although the Hatch-Waxman Act's goal was to get low-cost generic drugs to consumers, it did not exchange safety for reduced prices. The Hatch-Waxman Act was intended to be a win-win situation in which generic drugs would be approved more quickly with no decrease in safety or effectiveness.

In crafting a law to increase drug-price competition, Congress focused on market entry, not on post-entry regulation. The Hatch-Waxman Act does not detail generic drug manufacturers' duties after the drug is approved or absolve them of responsibility for the safety of the drugs they manufacture. Indeed, at hearings on the legislation, representatives of the generic drug industry recognized their continuing responsibility for their products after approval. For example, Kenneth N. Larsen, the chairman of the Generic Pharmaceutical Industry Association, stated that generic drug companies were "sensitive to the importance of looking at adverse reactions." *Drug Legislation: Hearings on H.R. 1554 and H.R. 3605 Before the Subcomm. on Health and the Env't of the House Comm. on Energy and Commerce*, 98th Cong. 45 (July 25, 1983). "The generic manufacturers of today will respond to those needs," he continued. "If it demands a higher level of knowledge on our part we are prepared to meet and respond to the need." *Id.* Larsen repeated the assurance of drug company responsibility in response to a

question from Representative Waxman about whether the NDA holders were better able to correct problems than generic companies. After acknowledging that the companies that performed the research would have more intimate knowledge of the drug, Larsen assured Mr. Waxman:

> I can state for my company as well as I think I can state for the other generic companies that produce these products, that we will do and provide whatever is required to be performed to meet the regulatory requirement to provide for the safety and well-being of those that are using the drug, this is our role and responsibility. This is an obligation to be in this business.

Id. at 47–48.

Similarly, Bill Haddad, executive officer and president of the Generic Pharmaceutical Industry Association, called concerns about whether generic drug companies would adequately report adverse events a "red herring." *Id.* at 50. "There seems to be a misconception about [] generic drug companies," he noted. "We also put our money into research. Every single generic drug company that I know has a large research staff. It not only researches the drug that they are copying, or bringing into the market but it researches new drugs, researches adverse reactions." *Id.* at 50-51. And in response to a question about whether generic drug companies were responsible for reporting adverse event reactions to the FDA, Milton A. Bass, General Counsel to the National Association of Pharmaceutical Manufacturers, which represented

generic drug companies, responded: "Not only yes, Mr. Chairman, but they should be." *Id.* at 47.

In discussing the importance of the Hatch-Waxman Act during the legislative process, members of Congress emphasized their intent to benefit American consumers, particularly older Americans. "Most importantly," Representative Skelton explained in discussing the bill on the House floor, "making generic drugs more available offers some relief to the millions of older Americans whose budgets are strained because medicare does not cover the cost of outpatient drugs. . . . Giving seniors the option of purchasing lower-priced generic drugs is imperative." 130 Cong. Rec. 24437 (Sept. 6, 1984). "Everyone in this country will benefit by enactment of this legislation," Representative Minish agreed, "but I feel it is particularly important that our senior citizens who fill more prescriptions than other segments of our population, can save money on their medical bills." *Id.* at 24456. "This is important legislation," Representative Fish noted. "[I]t is important to the consumer, especially the elderly." *Id.* at 24428.

This Court recently noted that, in enacting the FDCA and its amendments, Congress "determined that widely available state rights of action provided appropriate relief for injured consumers" and "may also have recognized that state-law remedies further consumer protection by motivating manufacturers to produce safe and effective drugs and to give adequate warnings." *Wyeth*, 129 S. Ct. at 1199-2000. Congress gave no indication that, in seeking to benefit American consumers through lower drug prices, it intended to decrease generic drug companies' incentives to ensure that their drugs are safe, effective, and contain

adequate warnings, or to deny consumers the ability to seek compensation for injuries caused by drugs with inadequate warnings. Under petitioners' position, however, generic drug manufacturers would have no incentive to ensure that their drugs contain adequate warnings, because they could not be held accountable if their drugs did not.

Moreover, consumers would have no remedies for injuries incurred as a result of inadequate warnings. Many courts, including the Eighth Circuit below, have held as a matter of state law that consumers injured by inadequately labeled generic drugs have no claims against the name-brand manufacturer, because they were not injured by that manufacturer's drug. *See, e.g.*, JA 418-21; *Foster v. Am. Home Prods. Corp.*, 29 F.3d 165 (4th Cir. 1994); *Finnicum v. Wyeth, Inc.*, 708 F. Supp. 2d 616 (E.D. Tex. 2010); *Couick v. Wyeth, Inc.*, 691 F. Supp. 2d 643 (W.D.N.C. 2010); *Swicegood v. Pliva, Inc.*, 543 F. Supp. 2d 1351 (N.D. Ga. 2008); *but see Conte v. Wyeth, Inc.*, 85 Cal. Rptr. 3d 299 (Cal. Ct. App. 2008). Yet, according to petitioners, injured consumers should also be denied an opportunity to seek compensation from the company that manufactured the drug that they did take. As the Fifth Circuit noted below, however, it would be "bizarre" to hold that "Congress intended to implicitly deprive a plaintiff whose doctor prescribes a generic drug of *any* remedy, while under *Levine*, that same plaintiff would have a state-law claim had she only demanded a name brand drug instead." JA 563.

Because Hatch-Waxman's goal was to get *safe* generic drugs into consumers' hands, state-law failure-to-warn claims against generic drug companies further the Act's

purposes, helping to ensure that the companies take reasonable steps to ensure that their drugs contain proper warnings and, therefore, can be used safely. In contrast, denying injured consumers of generic drugs compensation for their injuries would be contrary to the purposes of the Act. In enacting Hatch-Waxman, Congress recognized the importance of generic drugs and the savings that they bring to the public. If generic drug manufacturers are immune from liability, however, injured consumers would essentially be punished for using generic rather than name-brand drugs. Moreover, already, consumers often incorrectly believe that generic drugs are less safe than their name-brand counterparts. *See, e.g.*, FDA, *Facts and Myths About Generic Drugs*, www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/ucm167991.htm (noting the "myths" that "[p]eople who are switched to a generic drug are risking treatment failure," that "[g]eneric drugs cost less because they are inferior to brand name drugs," and that "[b]rand name drugs are safer than generic drugs"). Sending the message that generic drug companies are not accountable for the safety of their products would only further that belief.

II. Risks Associated With a Particular Drug Often Do Not Become Known Until Long After the Drug Has Been Approved.

Generic drugs do not enter the market until after the name-brand drug has been approved and its patent has expired. But the length of time between the initial approval of the name-brand drug and the approval of the generic drug does not ensure the drug's safety or that its label contains adequate warnings. Because risks often do

not become apparent until long after a drug has been approved by the FDA, it is vital that all drug manufacturers—including generic drug manufacturers—have incentives to respond to safety risks as they become known.

The safety of new drugs "cannot be known with certainty until a drug has been on the market for many years." Karen E. Lasser, et al., *Timing of New Black Box Warnings and Withdrawal for Prescription Medications*, 287 JAMA 2215 (2002). A study in the Journal of the American Medical Association on the frequency and timing of the discovery of adverse drug reactions (ADRs) requiring black-box warnings or drug withdrawal concluded that "only half of newly discovered serious ADRs are detected and documented in the *Physicians' Desk Reference* within 7 years after drug approval." *Id.* at 2218. The study noted that Pemoline, a central nervous system stimulant, received its first *Physicians' Desk Reference* black-box warning 22.9 years after it was approved; Danazol, a drug for infertility, received its first black-box warning 15.5 years after approval; and Disopyramide Phosphate, an antiarrhythmic, added its first black-box warning 19.3 years after approval. *Id.* at 2217. In November 2010, the FDA announced that the popular painkiller Propoxyphene (known by the brand names Darvon and Darvocet), which was first approved in 1957, would be removed from the market because of cardiac risks. *See* FDA, *Propoxyphene-Containing Products*, www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm233800.htm. In 2007, 21.3 million prescriptions had been filled for the generic combination of propoxyphene and

acetaminophen, making it one of the most-prescribed generic drugs in the United States. *See* Sidney M. Wolfe, M.D., *Testimony on Propoxyphene (Darvon) Before FDA's Anesthetic, Analgesic and Rheumatologic Drugs and Drug Safety and Risk Management Advisory Committees* (Jan. 30, 2009), *available at* www.citizen.org/Page.aspx?pid=537.

The long history of a black-box warning recently placed on fluoroquinolone antibiotics such as Cipro demonstrates how warnings can change over time, including after both name-brand and generic drugs are approved. The first floroquinolone drug was approved by the FDA in 1986. Over the following years there were reports of tendon inflammation and rupture associated with fluoroquinolones. Based on these reports, in 1996, *amicus curiae* Public Citizen successfully petitioned the FDA to place a warning regarding the risk of tendinopathy and tendon injury on the package insert of fluoroquinolone drugs. *See* Public Citizen, *Petition to Require a Warning on All Fluoroquinolone Antibiotics* (Aug. 1, 1996), *available at* www.citizen.org/hrg1399. The warning was in plain type alongside a list of other risks. Thereafter, however, fluoroquinolone-induced tendon injures continued to occur at an alarming rate. Thus, in 2008, FDA notified manufacturers of the need to add a black-box warning to their labels. *See* FDA, *Information for Healthcare Professionals: Fluoroquinolone Antimicrobial Drugs* (July 8, 2008), *available at* www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm126085.htm. This black-box warning was added more than 20 years after the approval of the

first name-brand fluoroquinolone drug, and years after generic versions came on the market.

Because new knowledge can require new warnings, drug manufacturers must take reasonable steps to ensure that their drugs are adequately labeled. As the Court noted in *Wyeth*, "[t]he FDA has limited resources to monitor the 11,000 drugs on the market, and manufacturers have superior access to information about their drugs, especially in the postmarketing phase as new risks emerge." 129 S. Ct. at 1202; *see also, e.g., id.* at 1202 n.11 (citing studies showing that FDA resources are inadequate for it to meet its regulatory responsibilities). And although the Food and Drug Administration Amendments Act of 2007 gave the FDA additional resources for drug safety and new authority to compel manufacturers to make labeling changes, *see* Pub. L. No. 110-85, 121 Stat. 823 (2007), "the resources of the drug industry to collect and analyze postmarket safety data vastly exceed the resources of the FDA, and no matter what we do, they will always have vastly greater resources to monitor the safety of their products than the FDA does." 153 Cong. Rec. S11832 (daily ed. Sept. 20, 2007) (Statement of Sen. Kennedy).

Generic drug companies are often in the best position to discover, assess, and take early action to address risks that come to light after the name-brand drug's period of patent exclusivity has ended because, once generic drugs are available, they often have the majority market share for the drug. Overall, approximately 70 percent of prescriptions are filled with generic drugs. *See, e.g.*, FDA, *Facts and Myths About Generic Drugs.* Generic drug manufacturers are already subject to the same

requirements as name-brand drugs regarding the "reporting and recordkeeping of adverse drug experiences." 21 C.F.R. § 314.98(a). They should not be immune from liability under state law if they fail to take reasonable steps to ensure that consumers are properly warned about risks from their products.

III. Generic Drug Manufacturers Can Act to Warn Consumers About the Dangers of Their Drugs.

Respondents' state-law claims allege that petitioners failed to take reasonable care to adequately warn patients of the risks associated with their products. The parties disagree about the scope of generic manufacturers' authority to alter their labels, but they agree that generic manufacturers can take some actions, such as asking the FDA to require a labeling change or to send out a "Dear Doctor" letter. *See* Pliva Br. 48. Indeed, the FDA has advised that, "[a]fter approval of an ANDA, if an ANDA holder believes that new safety information should be added [to a product's labeling], it should provide adequate supporting information to FDA." 57 Fed. Reg. 17950, 17961 (Apr. 28, 1992). State-law claims seeking to hold a generic drug manufacturer accountable for failing to take action that a reasonable manufacturer would take to warn patients of dangers associated with its product—actions that are allowed, even encouraged, by the federal regulatory scheme—are wholly consistent with the goals of and duties imposed by that scheme.

Petitioners note that even if generic manufacturers asked for a warning or a Dear Doctor letter, the FDA might say no. To be sure, on the merits, petitioners may explain the restrictions and obligations of the federal

regulatory scheme and show their compliance with that scheme in support of their arguments that they took reasonable care to warn patients about the risks of metoclopramide. The law of every state allows such evidence and, in some states, requires that it be given substantial weight. *See, e.g., Restatement (Third) of Torts: Prod. Liab.* § 4; 63B Am. Jur. 2d *Prods. Liab.* § 1922 ("As a general rule, compliance with applicable federal standards is relevant but not conclusive evidence in a products liability case."). In this way, the federal regulatory scheme can play an important role in litigating state-law failure-to-warn claims against drug manufacturers.

But the issue here is preemption. Petitioners argue that the regulatory scheme must be preemptive because litigating the case on the merits may require speculation about how the FDA would have responded to manufacturers' efforts to revise the labeling. *See* Pliva Br. 49. Name-brand manufacturers, however, also must seek FDA approval for labeling changes. Yet, in *Wyeth*, the Court held that "absent clear evidence that the FDA would not have approved a change to Phenergan's label, we will not conclude that it was impossible for Wyeth to comply with both federal and state requirements." 129 S. Ct. at 1198; *see also id.* (noting that the manufacturer "offered no such evidence"). By declining to hold failure-to-warn claims preempted, while recognizing that drug manufacturers might submit evidence of whether the FDA would have approved a label change, the Court recognized that state-law claims are not preempted whenever they might involve "speculation about what a federal agency would have done in hypothetical proceedings." Pliva Br. 53.

Petitioners attempt to distinguish *Wyeth* on the ground that name-brand manufacturers can change labeling under the "changes being effected" (CBE) process, which allows manufacturers to add or strengthen a warning without prior approval from the FDA, 21 C.F.R. § 314.70(c)(6)(iii)(A), and that, therefore, "the brand manufacturer's new warnings could have reached consumers without FDA action." Pliva Br. 53. Even assuming that the FDA does not allow CBE changes for generic drugs, however, petitioners are wrong to portray the CBE process as giving manufacturers the ability to make labeling changes without FDA involvement. The CBE process simply allows the drug manufacturer to make the change while the request for permission to revise the labeling is pending, instead of requiring the drug manufacturer to obtain advance approval. *See* 21 C.F.R. § 314.70(c)(6). Thus, even in cases in which changes are made through the CBE process, the FDA may reject the request for a change, just as it might reject a change suggested by a generic drug manufacturer. *Id.* § 314.70(c)(7). Yet *Wyeth* does not hold that claims are preempted because the FDA *might* reject a change made under the CBE process; it concludes that claims are not preempted absent clear evidence that the FDA would not have approved a labeling change. Accordingly, petitioners' "speculation" objection is inconsistent with *Wyeth*.

Citing *Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341 (2001), petitioners also argue that state-law claims based on manufacturers' failure to take actions such as alerting the FDA to a newly discovered safety risk would "impose extraordinary burdens on the Agency" by "draw[ing] [it] into nationwide litigation." *Id.* at 55.

Notably, the FDA appears not to share petitioners' concerns. Although the United States stated in its petition-stage brief that "the court of appeals appeared to anticipate that the parties could litigate on remand the question of what action FDA would have taken in response to a hypothetical warning proposal from petitioners," it concluded that state-law failure-to-warn claims are not categorically preempted and recommended denying the petition. Br. of the U.S. as *Amicus Curiae* at 10, 20. And although petitioners imply that FDA employees will be forced to spend large amounts of time testifying, Pliva Br. 56-58, FDA regulations provide that employees may not "give any testimony before any tribunal pertaining to any function" of the FDA, "except as authorized by the Commissioner of Food and Drugs." 21 C.F.R. § 20.1; *see generally United States ex rel. Touhy v. Ragen*, 340 U.S. 462 (1951).

Petitioners also contend that allowing claims based on manufacturers' failure to take actions such as asking the FDA for a label change should be preempted because they would cause generic drug companies to "inundate FDA with a deluge of submissions" that it "neither wants nor needs." Pliva Br. 30 (quoting *Buckman*, 531 U.S. at 351). But information about safety risks is information that the FDA *does* want and need. Indeed, the FDA has instructed manufacturers that "if an ANDA holder believes that new safety information should be added, it should provide adequate supporting information to FDA." 57 Fed. Reg. at 17961. And petitioners' threat that they and other manufacturers will send "meritless" labeling-change requests to the FDA, Pliva Br. 60, is disingenuous. Generic drug companies are unlikely to ask the FDA to

add unnecessary warnings for fear that the FDA might comply with their requests. Moreover, the argument that allowing claims to proceed would cause drug companies to inundate the FDA with proposed labeling changes was made, and implicitly rejected, in *Wyeth*. *See* Br. for PhRMA and BIO as *Amici Curiae* Supporting Pet. at 36-38, in *Wyeth v. Levine*, No. 06-1249.

In any event, the question in determining preemption is not whether manufacturers' efforts to comply with state-law duties might lead to additional regulatory submissions. Rather, the question is whether the state-law claims and the regulatory scheme conflict. Here, there is no such conflict. If a generic drug manufacturer does not take the steps allowed by the regulatory scheme to provide adequate warnings, it should not be permitted to hide behind that scheme to avoid accountability for its actions.

CONCLUSION

The judgments below should be affirmed.

Respectfully submitted,

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AMICUS CURIAE BRIEF

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IN THE

Supreme Court of the United States

PLIVA, INC. ET AL., *Petitioners*,

v.

GLADYS MENSING, *Respondent*.

ACTAVIS ELIZABETH, LLC, *Petitioner*,

v.

GLADYS MENSING, *Respondent*.

ACTAVIS, INC., *Petitioner*,

v.

JULIE DEMAHY, *Respondent*.

ON WRITS OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FIFTH AND EIGHTH CIRCUITS

BRIEF OF REP. HENRY A. WAXMAN AS *AMICUS CURIAE* IN SUPPORT OF RESPONDENTS URGING AFFIRMANCE

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BRIEF OF REP. HENRY A. WAXMAN AS *AMICUS CURIAE* IN SUPPORT OF RESPONDENTS URGING AFFIRMANCE

INTEREST OF *AMICUS CURIAE*

Amicus curiae Rep. Henry A. Waxman is a Member of Congress with an important interest in this case.[1] Rep. Waxman is ranking Member of the House Committee on Energy and Commerce, which has principal responsibility for legislation and oversight in the areas of public health, consumer protection, and food and drug safety. Rep. Waxman is a committed advocate for consumer protection and was a co-author and leading sponsor of the statute at issue in this case, the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (Hatch-Waxman Amendments).

Rep. Waxman is proud of the benefits generated by the Hatch-Waxman Amendments for American consumers. In 1984, just 19 percent of the prescription drugs in the United States were generic.[2]

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[1] This brief has been filed with the written consent of the parties, which is on file with the Clerk of Court. Pursuant to Rule 37.6, *amicus* affirms that no counsel for a party authored this brief in whole or in part, nor did any person or entity, other than *amicus* or his counsel, make a monetary contribution to the preparation or submission of this brief.

[2] Congressional Budget Office, HOW INCREASED COMPETITION FROM GENERIC DRUGS HAS AFFECTED PRICES AND RETURNS IN THE PHARMACEUTICAL INDUSTRY 1 (July 1998) (CBO Report).

Today, generic drugs account for 70 percent of the prescriptions filled in this country.[3] Generic drugs have played an important role in holding down national spending on prescription pharmaceuticals and have saved consumers many billions of dollars.[4] Research shows that, on average, the cost of a generic drug is 80 to 85% lower than the brand-name product.[5]

Amicus has an important perspective on the question presented. He is a strong supporter of the generic drug industry. This ongoing commitment does not, however, detract from his belief that in enacting the Hatch-Waxman Amendments, Congress did not intend to categorically preempt state-law failure-to-warn claims.

At bottom, this case presents a question of congressional intent. This Court has explained that "[t]he purpose of Congress is the ultimate touchstone in every pre-emption case." *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996) (citation and internal quotation marks omitted); *see also Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 516 (1992) (same). *Amicus* is uniquely situated to address the question of congressional intent at the center of this case.

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[3] Susan Okie, "Multinational Medicines-Ensuring Drug Quality in an Era of Global Manufacturing," 361 NEW ENG. J. MED. 737, 738 (2009).

[4] CBO Report at 1.

[5] Food and Drug Administration, "Facts and Myths About Generic Drugs," available at http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/ucm167991.htm.

Although *amicus* submits this brief in his individual capacity, his views are informed by his experiences as a Member of Congress.

SUMMARY OF ARGUMENT

The Hatch-Waxman Amendments do not categorically preempt state-law failure-to-warn claims. Such claims are generally consistent with the purposes of the Amendments -- to benefit consumers by bringing safe and effective low-cost generic drugs to market. Nothing in the legislative history of the Amendments manifests any congressional intent to abolish all state-law failure-to-warn remedies for injured consumers. Had Congress intended to take that momentous step, it would have issued a clear statement that state law was preempted. At its core, "[p]re-emption fundamentally is a question of congressional intent." *English v. General Elec. Co.*, 496 U.S. 72, 78 (1990). Congress did not intend to preempt all failure-to-warn claims involving generic drugs.

Nor would it be "physically impossible" for generic drug manufacturers to comply with federal law and their state-law duties. Although a generic drug label must be the same as its brand-name counterpart, there are other bases for imposing failure-to-warn liability on generic manufacturers. For example, generic drug makers have the same responsibility as brand-name manufacturers to inform the FDA of any new information about risks that may require a change in the labeling of their drugs. They can also request that the FDA send a "Dear Health Care Professional" letter or coordinate a campaign of such letters, in order to advise physicians and others of

newly available information. If generic manufacturers fail to take such steps, requiring them to pay damages under state law in a failure-to-warn case creates no inconsistency with federal law.

Categorical preemption of failure-to-warn claims would deprive consumers of generic drugs of a remedy available to consumers of brand-name drugs under *Wyeth v. Levine*, 129 S. Ct. 1187 (2009), in which this Court held that state-law failure-to-warn claims against brand-name manufacturers are not preempted. Although there are important differences in the regulatory treatment of brand-name and generic drugs, this Court's reasoning in *Levine* militates against categorical preemption here. In particular, this Court's recognition of the longstanding coexistence of state tort remedies and federal regulation of prescription drugs demonstrates that the two systems are in general complementary.

Moreover, petitioners' position in this case would create the peculiar situation in which a plaintiff whose doctor prescribes a generic drug would be deprived of a remedy for a failure-to-warn claim, while under *Levine*, the same plaintiff would be able to bring a state-law claim if he or she had demanded a brand-name drug instead, or if the doctor had chosen to prescribe a brand-name drug without asking the patient. Congress did not intend that use of generic drugs would come at the price of losing a traditional compensatory tort remedy under state law. Given the fact that generic drugs now account for seven out of ten prescriptions filled in the United States, carving out an exception to *Levine* for generic drugs would dramatically weaken the force and reduce the scope of that decision and, at the same

time, leave millions of consumers without any ability to seek a remedy for their injuries.

ARGUMENT

This Court has made clear that a state tort claim is preempted if it is impossible for a defendant to satisfy both its state-law obligation and federal regulatory requirements. *Levine*, 129 S. Ct. at 1196. In addition, "[u]nder ordinary conflict preemption principles a state law that 'stands as an obstacle to the accomplishment and execution of the full purposes and objectives' of a federal law is pre-empted." *Williamson v. Mazda Motor of America, Inc.*, No. 08-1314, slip op. at 5 (Feb. 23, 2011) (quoting *Hines v. Davidowitz*, 312 U.S. 52, 67 (1941)).

In this case, holding a generic manufacturer liable on a failure-to-warn theory would not impermissibly frustrate the purposes of the Amendments. Nor is there a conflict between a generic manufacturer's duties under state law and the requirements of the Hatch-Waxman Amendments that would warrant a categorical preemption of failure-to-warn claims against generic drug manufacturers.

I. State-Law Failure-To-Warn Claims Are Consistent With The Purposes Of The Hatch-Waxman Amendments.

The Food, Drug and Cosmetics Act (FDCA) requires that manufacturers obtain premarket regulatory approval for all prescription pharmaceuticals before they are introduced into commerce. 21 U.S.C. § 355(a). Manufacturers of new drugs must submit a new drug application (NDA) to

the FDA. *Id.* at § 355(b). The FDA has codified the NDA regulations at 21 C.F.R. Part 314. An NDA must contain, *inter alia*, scientific data demonstrating the drug's effectiveness and safety for its intended use; a statement of the drug's components; and examples of proposed labeling for the drug. *See* 21 U.S.C. § 355; 21 C.F.R. § 314.105(b). "Before approving an NDA ... [the] FDA undertakes a detailed review of the proposed labeling, allowing only information for which there is a scientific basis to be included in the FDA-approved labeling." 73 Fed.Reg. 49603, 49604 (2008). The FDA will reject the proposed labeling if "based on a fair evaluation of all material facts, such labeling is false or misleading in any particular." *See* 21 U.S.C. § 355; 21 C.F.R. § 314.105(b).

In 1984, Congress enacted the Hatch-Waxman Amendments to the FDCA, which established the federal regulatory framework governing generics.[5] The House Energy and Commerce Committee Report cited "the policy objective" of the bill as "getting *safe* and *effective* generic substitutes on the market as quickly as possible after the expiration of the patent." H. Rep. No. 98-857, pt. 2, 98th Cong. 2d sess. 9 (1984) (emphasis added). The sponsors of the Amendments also stressed the pro-consumer nature of the bill. Rep. Waxman explained:

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130 Cong. Rec. 24430 (Sept. 6, 1984) (statement of Rep. Waxman). Sen. Hatch added:

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Id. at 15847 (June 12, 1984) (statement of Sen. Hatch) (emphasis added).

Under the Amendments, once a brand-name drug has been approved by FDA, any drug company may seek permission to market a generic version through a significantly simplified process, known as the abbreviated new drug application procedure, or ANDA. *See* 57 Fed.Reg. 17950, 17951 (1992). ANDA drugs must be the "same as" a name brand drug that has already been approved by the FDA as to active ingredients, route of administration, dosage form, strength, and conditions of use recommended in the labeling. 21 U.S.C. § 355(j)(2)(A)(iii). Generic drug manufacturers need not repeat the clinical work of their brand counter-parts, but instead must establish only the generic drug's bioequivalence with the name brand drug. *Id.* at § 355(j)(2)(A)(iv). The ANDA must also show that the "labeling proposed for the [generic] drug is the same as the labeling approved for" the brand-name drug. *Id.* at § 355(j)(2)(A)(v).[7]

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[7] The FDA permits certain minor differences in labeling between brand-name drugs and generics that are not at issue here. 21 C.F.R. § 314.94(a)(8)(iv).

The ANDA process set forth in the Hatch-Waxman Amendments was premised on the idea that a generic pharmaceutical would be shown to be the *same as* the brand-name drug in every significant way — including the labeling. As the House Energy and Commerce Committee Report explained, "[g]eneric copies of any drugs may be approved if the generic is the same as the original drug or so similar that FDA has determined the differences do not require safety and effectiveness testing." H. Rep. No. 98-857, pt. 1, 98th Cong. 2d sess. 14-15 (1984). "[T]he focus of the bill is to provide the [FDA] with sufficient information to assure that the generic drug is the same as the listed drug that has previously been determined to be safe and effective." *Id.* at 21. "[A]n ANDA must contain adequate information to show that the proposed labeling for the generic drug is the same as that of the listed drug." *Id.* at 22.

The 27 years since the enactment of the Hatch-Waxman Amendments have proven the law to be a resounding and spectacular success. Generic medicines are now considered to be a critical component of quality health care and promoting the public health. They advance competition, which lowers drug prices. Lower drug prices reduce the nation's overall health care bill. Indeed, today, a remarkable 70 percent of prescriptions are filled with generic medicines – saving consumers and the federal and state governments tens of billions of dollars annually.[5] Most importantly, lower drug prices

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translate into access to life-saving and life-enhancing drugs for many patients who might not otherwise be able to afford their medications.

The success of the Hatch-Waxman Amendments rests primarily with the law's core principle — the assurance of "sameness" between brand and generic drugs, which provides confidence to consumers that generics will be every bit as safe and effective as brand-name drugs. A key component of this "sameness" principle is that manufacturers of generic drugs will be held to the same high standards as brand-name drugs and that any violation of these standards can be addressed with an identical set of legal tools.

As a practical matter, Congress could not have intended it any other way. Consumers' legal rights would have to be protected in the same way regardless of which kind of drug they take. If not, their ability to seek redress in court would depend upon the type of medication that was prescribed, a choice many consumers are not given by either their health plan or their circumstances in life. Congress did not intend for consumers' rights to be categorically eliminated simply because they purchased a generic rather than a brand-name drug.

As a matter of policy, Congress also did not intend such an outcome. Nothing in the legislative history of the Amendments manifests any congressional intent to leave consumers of generics without any remedy in the event of injury.

(2010) (available at http://www.gphaonline.org/sites/default/files/AnnualReport2010.pdf).

The fact that there is no express preemption provision in the Hatch-Waxman Amendments mirrors the primacy of this "sameness" principle. Congress recognized that the success of these Amendments would depend upon the extent to which consumers are confident that brand-name and generic drugs are the same and are treated the same. To take away an injured consumer's right to a state-law tort remedy simply because she happened unwittingly to take a generic rather than a brand-name drug would constitute an undoing of the very underpinning — the principle of sameness — on which the Amendments were built. This, in turn, would threaten the overall prospects for success of the legislation.

II. There Is No Conflict Between The Hatch-Waxman Amendments And State Law That Would Warrant a Categorical Preemption of Claims Against Generic Drug Manufacturers.

Petitioners have insisted that state-law tort liability for a generic drug manufacturer in a failure-to-warn case is categorically preempted because the manufacturer cannot comply with its labeling duties under both the Hatch-Waxman Amendments and state law. That argument sweeps too broadly. Although a generic drug label must be the same as its brand-name counterpart, there are other bases for imposing failure-to-warn liability on generic manufacturers.

For example, generic drug makers can and should — and, indeed, do — provide the FDA with any new information they obtain regarding safety hazards

associated with their products, just as brand-name manufacturers do.[9] If a generic manufacturer fails to inform the FDA of such new developments, requiring it to pay damages under state law in a failure-to-warn case creates no inconsistency with federal law and is not preempted.

This is especially true given the basic record-keeping and reporting requirements with which both brand-name and generic manufacturers must comply.

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[9] At hearings on the Hatch-Waxman Amendments, representatives of the generic drug industry stressed that they were willing to keep FDA informed of the risks of their products. *See* New Drug Application: Hearings on H.R. 3605, The Drug Price Competition Act, House Committee on Energy & Commerce, Subcommittee on Health and the Environment, 98th Cong., 1st sess. 45 (July 15, 1983) ("I, too, would like to comment on this adverse reaction issue that was brought up. I can speak as a manufacturer and for two other generic companies in whose representatives are in attendance that are sensitive to the importance of looking at adverse reactions. We are sensitive and responsible. The generic manufacturers of today will respond to those needs. As far as I know we have not been remiss in that responsibility. If it demands a higher level of knowledge on our part we are prepared to meet and respond to the need.") (testimony of Kenneth N. Larsen, chairman of the Generic Pharmaceutical Industry Association); *id.* at 50-51 ("[G]eneric companies . . . also put our money into research. Every single generic drug company that I know has a large research staff. It not only researches the drug that they are copying, or bringing into the market but it researches new drugs, researches adverse reaction.") (testimony of Mark Haddad, member of the board of directors of the Generic Pharmaceutical Industry Association).

Both brand-name and generic manufacturers are statutorily required to keep records of clinical experiences and ensure that their products remain safe and effective as labeled. 21 U.S.C. § 355(k). FDA regulations mandate that all manufacturers record and report adverse events. 21 C.F.R. § 314.80(a) and (c) (brand-name manufacturers); *id.* at § 314.98(a) (generic manufacturers). Manufacturers must submit annual reports including, *inter alia*, a "summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product" and a "description of actions the applicant has taken or intends to take as a result of this new information." *Id.* at § 314.81(b)(2)(i).

In commentary accompanying the FDA's implementation of the Hatch-Waxman Amendments, the FDA stated:

> If an ANDA applicant believes new safety information should be added to a product's labeling, it should contact FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised. After approval of an ANDA, if an ANDA holder believes that new safety information should be added, it should provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised.

57 Fed.Reg. 17950, 17961 cmt. 40 (Apr. 28, 1992).

A generic manufacturer that becomes aware of safety issues can also use a "Dear Health Care Professional" (DHCP) letter to warn physicians and

others of the risks associated with the drug. *See* 21 C.F.R. § 200.5 (setting standards for such letters). A generic manufacturer can take steps to work together with the FDA to ensure that such a letter is distributed to health care professionals. The manufacturer can request that the FDA send out a letter or that the agency otherwise coordinate a DHCP letter campaign.[10]

The responsibility of both the brand-name and generic drug manufacturers to alert the FDA to new safety hazards is a critical one, so that the agency can ensure that labels accurately reflect the most up-to-date information and can also ensure consistency between the treatment of brand-name drugs and their generic equivalents. As this Court noted in *Levine*, "risk information [regarding pharmaceuticals] accumulates over time and that the same data may take on a different meaning in light of subsequent developments." 129 S. Ct. at 1197. The Court further noted that "[t]he FDA has limited resources to monitor the 11,000 drugs on the market, and manufacturers have superior access to information about their drugs, especially in the postmarketing phase as new risks emerge." *Id.* at 1202.

To be sure, generic drug manufacturers do not conduct or replicate the full clinical trials necessary for the initial approval of a brand-name drug, nor are they expected to do so, because it could well prevent

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[10] DHCP letters are considered a form of "labeling" under the FDCA, 21 U.S.C. § 321(m), and therefore are subject to FDA review and regulation to ensure that they are not false or misleading. *See id.* at § 352(a); 21 C.F.R. § 201.100(d)(1); *id.* at § 314.150(b)(3).

them from bringing a lower-cost generic version to market. *See* H. Rep. No. 98-857, pt. 1, 98th Cong. 2d sess. 16 (1984). But generic manufacturers often receive important risk information once their drug is on the market, and they should be treated the same as brand-name manufacturers with respect to their responsibility to bring relevant data to the FDA's attention.

There is no conflict between federal law and state failure-to-warn liability of generic drug manufacturers that would warrant a categorical preemption of all claims against them. It is clear that a generic and a brand-name label must be the same and that a generic firm cannot unilaterally change its label. To permit individual generic drug labels to differ significantly from their brand-name counterparts—particularly with respect to safety information—would thwart the "sameness" goal reflected in the Hatch-Waxman Amendments. However, it is not only possible for a generic manufacturer in possession of important risk information to take steps to notify FDA that a labeling change may be necessary, but it is, in fact, also encouraged and recommended by FDA. Therefore, generic manufacturers can fulfill both federal and state law in this respect; indeed, it is essential that they do so to fulfill the Hatch-Waxman goals of ensuring drug safety and consumer protection.

III. This Court's Reasoning In *Wyeth v. Levine* Is Applicable To Generic Drugs.

In *Levine*, this Court held that the FDCA did not preempt state-law failure-to-warn claims against

brand-name manufacturers. The Hatch-Waxman Amendments and their legislative history confirm that this Court's reasoning in *Levine* can be applied in certain respects to suits involving generic drug makers as well. *Levine* recognized that drug manufacturers bear a key responsibility for collecting and transmitting information regarding the safe and effective use of their products. In fact, this Court found that multiple reports of adverse drug experiences provided the substantiation necessary to justify a request for a heightened warning. 129 S. Ct. at 1197.

This Court's reasoning in *Levine* is instructive. The Court began with the fundamental assumption, equally salient here, "that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress." 129 S. Ct. at 1194-95. This Court noted the longstanding coexistence of state tort remedies and federal regulation of prescription drugs:

> If Congress thought state-law suits posed an obstacle to its objectives, it surely would have enacted an express pre-emption provision at some point during the FDCA's 70-year history. But despite its 1976 enactment of an express pre-emption provision for medical devices, ... Congress has not enacted such a provision for prescription drugs.... Its silence on the issue, coupled with its certain awareness of the prevalence of state tort litigation, is powerful evidence that Congress did not intend FDA oversight to be the

> exclusive means of ensuring drug safety and effectiveness.

Id.

In particular, the Court explained that "failure-to-warn actions ... lend force to the FDCA's premise that manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times." *Id.* at 1202. Congress "determined that widely available state rights of action provided appropriate relief for injured [drug] consumers" and that "state-law remedies further consumer protection by motivating manufacturers ... to give adequate warnings." *Id.* at 1199-1200.

This Court observed that Congress and the FDA have viewed state tort law as complementing, not obstructing, the goals of the FDCA. "In keeping with Congress' decision not to pre-empt common-law tort suits, it appears that the FDA traditionally regarded state law as a complementary form of drug regulation." *Id.* at 1202.

Congress understands that state tort law is an indispensable partner to federal safety regulation. "The case for federal pre-emption is particularly weak where Congress has indicated its awareness of the operation of state law in a field of federal interest, and has nonetheless decided to 'stand by both concepts and to tolerate whatever tension there [is] between them.'" *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 166-67 (1989) (quoting *Silkwood v. Kerr-McGee Corp.*, 464 U.S. 238, 256 (1984)).

Indeed, in the 1962 amendments to the FDCA, Congress expressly limited the preemptive effect of the statute by stating:

> Nothing in the amendments made by this Act to the Federal Food, Drug and Cosmetic Act shall be construed as invalidating any provision of State law which would be valid in the absence of such amendments unless there is a direct and positive conflict between such amendments and such provisions of State law.

Drug Amendments of 1962 (Harris-Kefauver Act), Pub. L. No. 87-781, § 202, 76 Stat. 780, 793 (1962). The plain language of this provision makes clear that the FDCA does not preempt state law in the absence of a "direct and positive" conflict. As this Court observed in *Levine*, "[a]s it enlarged the FDA's powers to 'protect the public health' and 'assure the safety, effectiveness, and reliability of drugs,' Congress took care to preserve state law." 129 S. Ct. at 1195-96 (internal citations omitted).

The Hatch-Waxman Amendments are part of this 70-year history and similarly do not categorically preempt failure-to-warn suits against generic manufacturers. There is no express preemption provision in the Amendments; rather, it is subject to the same saving provision enacted in 1962. If Congress had wished to depart from the usual rule governing other pharmaceuticals, it could have crafted a special preemption provision for generic drugs in its 1984 amendments. Congress is well aware of how to enact such special provisions. It did

so for medical devices in 1976,[11] for vaccines in 1986,[12] and for over-the-counter medications in 1997.[13]

In holding in *Bruesewitz v. Wyeth LLC*, No. 09-152 (Feb. 22, 2011), that the Vaccine Act of 1986 bars state-law design-defect claims against vaccine manufacturers, this Court reiterated that "we have previously expressed doubt that Congress would quietly preempt product-liability claims without providing a federal substitute." No. 09-152, slip op. at 16 (citing *Lohr*). In *Bruesewitz*, this Court observed that, in enacting the 1986 Vaccine Act, Congress deliberately departed from the regime applicable to pharmaceuticals and established a "no-fault compensation program 'designed to work faster and with greater ease than the civil tort system.'" *Id.* at 3 (citation omitted). In contrast, there is no similar no-fault compensation scheme available with respect to generic drugs, and no indication that Congress sought to displace traditional state-law tort remedies.

Establishing a categorical preemption of all state law claims against generic drug manufacturers would

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[11] *Riegel v. Medtronic, Inc.*, 552 U.S. 312 (2008) (considering the effect of the express preemption provision of the Medical Device Amendments of 1976, 21 U.S.C. § 360(k)(a)).

[12] *Bruesewitz v. Wyeth LLC*, No. 09-152 (Feb. 22, 2011) (construing 42 U.S.C. §300aa-22(b)(1), enacted as part of the National Childhood Vaccine Injury Act of 1986).

[13] In 1997, Congress preempted certain state requirements concerning over-the-counter medications but expressly preserved product liability actions. *See* 21 U.S.C. §§ 379r(e), 379s(d).

create a dangerous asymmetry because it would make the availability of a compensatory tort remedy depend upon the fortuity of whether a patient receives a prescription for a name brand or generic drug. In enacting the Hatch-Waxman Amendments, Congress did not intend to create a categorical exemption from failure-to-warn liability for generic manufacturers.

CONCLUSION

The judgments below should be affirmed

Respectfully submitted,

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Dated: March 2, 2011

Although *amicus* submits this brief in his individual capacity, his views are informed by his experiences as a Member of Congress.

SUMMARY OF ARGUMENT

The Hatch-Waxman Amendments do not categorically preempt state-law failure-to-warn claims. Such claims are generally consistent with the purposes of the Amendments -- to benefit consumers by bringing safe and effective low-cost generic drugs to market. Nothing in the legislative history of the Amendments manifests any congressional intent to abolish all state-law failure-to-warn remedies for injured consumers. Had Congress intended to take that momentous step, it would have issued a clear statement that state law was preempted. At its core, "[p]re-emption fundamentally is a question of congressional intent." *English v. General Elec. Co.*, 496 U.S. 72, 78 (1990). Congress did not intend to preempt all failure-to-warn claims involving generic drugs.

Nor would it be "physically impossible" for generic drug manufacturers to comply with federal law and their state-law duties. Although a generic drug label must be the same as its brand-name counterpart, there are other bases for imposing failure-to-warn liability on generic manufacturers. For example, generic drug makers have the same responsibility as brand-name manufacturers to inform the FDA of any new information about risks that may require a change in the labeling of their drugs. They can also request that the FDA send a "Dear Health Care Professional" letter or coordinate a campaign of such letters, in order to advise physicians and others of

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Categorical preemption of failure-to-warn claims would deprive consumers of generic drugs of a remedy available to consumers of brand-name drugs under *Wyeth v. Levine*, 129 S. Ct. 1187 (2009), in which this Court held that state-law failure-to-warn claims against brand-name manufacturers are not preempted. Although there are important differences in the regulatory treatment of brand-name and generic drugs, this Court's reasoning in *Levine* militates against categorical preemption here. In particular, this Court's recognition of the longstanding coexistence of state tort remedies and federal regulation of prescription drugs demonstrates that the two systems are in general complementary.

Moreover, petitioners' position in this case would create the peculiar situation in which a plaintiff whose doctor prescribes a generic drug would be deprived of a remedy for a failure-to-warn claim, while under *Levine*, the same plaintiff would be able to bring a state-law claim if he or she had demanded a brand-name drug instead, or if the doctor had chosen to prescribe a brand-name drug without asking the patient. Congress did not intend that use of generic drugs would come at the price of losing a traditional compensatory tort remedy under state law. Given the fact that generic drugs now account for seven out of ten prescriptions filled in the United States, carving out an exception to *Levine* for generic drugs would dramatically weaken the force and reduce the scope of that decision and, at the same

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This Court has made clear that a state tort claim is preempted if it is impossible for a defendant to satisfy both its state-law obligation and federal regulatory requirements. *Levine*, 129 S. Ct. at 1196. In addition, "[u]nder ordinary conflict preemption principles a state law that 'stands as an obstacle to the accomplishment and execution of the full purposes and objectives' of a federal law is pre-empted." *Williamson v. Mazda Motor of America, Inc.*, No. 08-1314, slip op. at 5 (Feb. 23, 2011) (quoting *Hines v. Davidowitz*, 312 U.S. 52, 67 (1941)).

In this case, holding a generic manufacturer liable on a failure-to-warn theory would not impermissibly frustrate the purposes of the Amendments. Nor is there a conflict between a generic manufacturer's duties under state law and the requirements of the Hatch-Waxman Amendments that would warrant a categorical preemption of failure-to-warn claims against generic drug manufacturers.

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translate into access to life-saving and life-enhancing drugs for many patients who might not otherwise be able to afford their medications.

The success of the Hatch-Waxman Amendments rests primarily with the law's core principle — the assurance of "sameness" between brand and generic drugs, which provides confidence to consumers that generics will be every bit as safe and effective as brand-name drugs. A key component of this "sameness" principle is that manufacturers of generic drugs will be held to the same high standards as brand-name drugs and that any violation of these standards can be addressed with an identical set of legal tools.

As a practical matter, Congress could not have intended it any other way. Consumers' legal rights would have to be protected in the same way regardless of which kind of drug they take. If not, their ability to seek redress in court would depend upon the type of medication that was prescribed, a choice many consumers are not given by either their health plan or their circumstances in life. Congress did not intend for consumers' rights to be categorically eliminated simply because they purchased a generic rather than a brand-name drug.

As a matter of policy, Congress also did not intend such an outcome. Nothing in the legislative history of the Amendments manifests any congressional intent to leave consumers of generics without any remedy in the event of injury.

(2010) (available at http://www.gphaonline.org/sites/default/files/ AnnualReport2010.pdf).

The fact that there is no express preemption provision in the Hatch-Waxman Amendments mirrors the primacy of this "sameness" principle. Congress recognized that the success of these Amendments would depend upon the extent to which consumers are confident that brand-name and generic drugs are the same and are treated the same. To take away an injured consumer's right to a state-law tort remedy simply because she happened unwittingly to take a generic rather than a brand-name drug would constitute an undoing of the very underpinning — the principle of sameness — on which the Amendments were built. This, in turn, would threaten the overall prospects for success of the legislation.

II. There Is No Conflict Between The Hatch-Waxman Amendments And State Law That Would Warrant a Categorical Preemption of Claims Against Generic Drug Manufacturers.

Petitioners have insisted that state-law tort liability for a generic drug manufacturer in a failure-to-warn case is categorically preempted because the manufacturer cannot comply with its labeling duties under both the Hatch-Waxman Amendments and state law. That argument sweeps too broadly. Although a generic drug label must be the same as its brand-name counterpart, there are other bases for imposing failure-to-warn liability on generic manufacturers.

For example, generic drug makers can and should — and, indeed, do — provide the FDA with any new information they obtain regarding safety hazards

associated with their products, just as brand-name manufacturers do.[9] If a generic manufacturer fails to inform the FDA of such new developments, requiring it to pay damages under state law in a failure-to-warn case creates no inconsistency with federal law and is not preempted.

This is especially true given the basic record-keeping and reporting requirements with which both brand-name and generic manufacturers must comply.

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[9] At hearings on the Hatch-Waxman Amendments, representatives of the generic drug industry stressed that they were willing to keep FDA informed of the risks of their products. *See* New Drug Application: Hearings on H.R. 3605, The Drug Price Competition Act, House Committee on Energy & Commerce, Subcommittee on Health and the Environment, 98th Cong., 1st sess. 45 (July 15, 1983) ("I, too, would like to comment on this adverse reaction issue that was brought up. I can speak as a manufacturer and for two other generic companies in whose representatives are in attendance that are sensitive to the importance of looking at adverse reactions. We are sensitive and responsible. The generic manufacturers of today will respond to those needs. As far as I know we have not been remiss in that responsibility. If it demands a higher level of knowledge on our part we are prepared to meet and respond to the need.") (testimony of Kenneth N. Larsen, chairman of the Generic Pharmaceutical Industry Association); *id.* at 50-51 ("[G]eneric companies . . . also put our money into research. Every single generic drug company that I know has a large research staff. It not only researches the drug that they are copying, or bringing into the market but it researches new drugs, researches adverse reaction.") (testimony of Mark Haddad, member of the board of directors of the Generic Pharmaceutical Industry Association).

Both brand-name and generic manufacturers are statutorily required to keep records of clinical experiences and ensure that their products remain safe and effective as labeled. 21 U.S.C. § 355(k). FDA regulations mandate that all manufacturers record and report adverse events. 21 C.F.R. § 314.80(a) and (c) (brand-name manufacturers); *id.* at § 314.98(a) (generic manufacturers). Manufacturers must submit annual reports including, *inter alia*, a "summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product" and a "description of actions the applicant has taken or intends to take as a result of this new information." *Id.* at § 314.81(b)(2)(i).

In commentary accompanying the FDA's implementation of the Hatch-Waxman Amendments, the FDA stated:

> If an ANDA applicant believes new safety information should be added to a product's labeling, it should contact FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised. After approval of an ANDA, if an ANDA holder believes that new safety information should be added, it should provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised.

57 Fed.Reg. 17950, 17961 cmt. 40 (Apr. 28, 1992).

A generic manufacturer that becomes aware of safety issues can also use a "Dear Health Care Professional" (DHCP) letter to warn physicians and

others of the risks associated with the drug. *See* 21 C.F.R. § 200.5 (setting standards for such letters). A generic manufacturer can take steps to work together with the FDA to ensure that such a letter is distributed to health care professionals. The manufacturer can request that the FDA send out a letter or that the agency otherwise coordinate a DHCP letter campaign.[10]

The responsibility of both the brand-name and generic drug manufacturers to alert the FDA to new safety hazards is a critical one, so that the agency can ensure that labels accurately reflect the most up-to-date information and can also ensure consistency between the treatment of brand-name drugs and their generic equivalents. As this Court noted in *Levine*, "risk information [regarding pharmaceuticals] accumulates over time and that the same data may take on a different meaning in light of subsequent developments." 129 S. Ct. at 1197. The Court further noted that "[t]he FDA has limited resources to monitor the 11,000 drugs on the market, and manufacturers have superior access to information about their drugs, especially in the postmarketing phase as new risks emerge." *Id.* at 1202.

To be sure, generic drug manufacturers do not conduct or replicate the full clinical trials necessary for the initial approval of a brand-name drug, nor are they expected to do so, because it could well prevent

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[10] DHCP letters are considered a form of "labeling" under the FDCA, 21 U.S.C. § 321(m), and therefore are subject to FDA review and regulation to ensure that they are not false or misleading. *See id.* at § 352(a); 21 C.F.R. § 201.100(d)(1); *id.* at § 314.150(b)(3).

them from bringing a lower-cost generic version to market. *See* H. Rep. No. 98-857, pt. 1, 98th Cong. 2d sess. 16 (1984). But generic manufacturers often receive important risk information once their drug is on the market, and they should be treated the same as brand-name manufacturers with respect to their responsibility to bring relevant data to the FDA's attention.

There is no conflict between federal law and state failure-to-warn liability of generic drug manufacturers that would warrant a categorical preemption of all claims against them. It is clear that a generic and a brand-name label must be the same and that a generic firm cannot unilaterally change its label. To permit individual generic drug labels to differ significantly from their brand-name counterparts—particularly with respect to safety information—would thwart the "sameness" goal reflected in the Hatch-Waxman Amendments. However, it is not only possible for a generic manufacturer in possession of important risk information to take steps to notify FDA that a labeling change may be necessary, but it is, in fact, also encouraged and recommended by FDA. Therefore, generic manufacturers can fulfill both federal and state law in this respect; indeed, it is essential that they do so to fulfill the Hatch-Waxman goals of ensuring drug safety and consumer protection.

III. This Court's Reasoning In *Wyeth v. Levine* Is Applicable To Generic Drugs.

In *Levine,* this Court held that the FDCA did not preempt state-law failure-to-warn claims against

brand-name manufacturers. The Hatch-Waxman Amendments and their legislative history confirm that this Court's reasoning in *Levine* can be applied in certain respects to suits involving generic drug makers as well. *Levine* recognized that drug manufacturers bear a key responsibility for collecting and transmitting information regarding the safe and effective use of their products. In fact, this Court found that multiple reports of adverse drug experiences provided the substantiation necessary to justify a request for a heightened warning. 129 S. Ct. at 1197.

This Court's reasoning in *Levine* is instructive. The Court began with the fundamental assumption, equally salient here, "that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress." 129 S. Ct. at 1194-95. This Court noted the longstanding coexistence of state tort remedies and federal regulation of prescription drugs:

> If Congress thought state-law suits posed an obstacle to its objectives, it surely would have enacted an express pre-emption provision at some point during the FDCA's 70-year history. But despite its 1976 enactment of an express pre-emption provision for medical devices, ... Congress has not enacted such a provision for prescription drugs.... Its silence on the issue, coupled with its certain awareness of the prevalence of state tort litigation, is powerful evidence that Congress did not intend FDA oversight to be the

> exclusive means of ensuring drug safety and effectiveness.

Id.

In particular, the Court explained that "failure-to-warn actions ... lend force to the FDCA's premise that manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times." *Id.* at 1202. Congress "determined that widely available state rights of action provided appropriate relief for injured [drug] consumers" and that "state-law remedies further consumer protection by motivating manufacturers ... to give adequate warnings." *Id.* at 1199-1200.

This Court observed that Congress and the FDA have viewed state tort law as complementing, not obstructing, the goals of the FDCA. "In keeping with Congress' decision not to pre-empt common-law tort suits, it appears that the FDA traditionally regarded state law as a complementary form of drug regulation." *Id.* at 1202.

Congress understands that state tort law is an indispensable partner to federal safety regulation. "The case for federal pre-emption is particularly weak where Congress has indicated its awareness of the operation of state law in a field of federal interest, and has nonetheless decided to 'stand by both concepts and to tolerate whatever tension there [is] between them.'" *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 166-67 (1989) (quoting *Silkwood v. Kerr-McGee Corp.*, 464 U.S. 238, 256 (1984)).

Indeed, in the 1962 amendments to the FDCA, Congress expressly limited the preemptive effect of the statute by stating:

> Nothing in the amendments made by this Act to the Federal Food, Drug and Cosmetic Act shall be construed as invalidating any provision of State law which would be valid in the absence of such amendments unless there is a direct and positive conflict between such amendments and such provisions of State law.

Drug Amendments of 1962 (Harris-Kefauver Act), Pub. L. No. 87-781, § 202, 76 Stat. 780, 793 (1962). The plain language of this provision makes clear that the FDCA does not preempt state law in the absence of a "direct and positive" conflict. As this Court observed in *Levine*, "[a]s it enlarged the FDA's powers to 'protect the public health' and 'assure the safety, effectiveness, and reliability of drugs,' Congress took care to preserve state law." 129 S. Ct. at 1195-96 (internal citations omitted).

The Hatch-Waxman Amendments are part of this 70-year history and similarly do not categorically preempt failure-to-warn suits against generic manufacturers. There is no express preemption provision in the Amendments; rather, it is subject to the same saving provision enacted in 1962. If Congress had wished to depart from the usual rule governing other pharmaceuticals, it could have crafted a special preemption provision for generic drugs in its 1984 amendments. Congress is well aware of how to enact such special provisions. It did

so for medical devices in 1976,[11] for vaccines in 1986,[12] and for over-the-counter medications in 1997.[13]

In holding in *Bruesewitz v. Wyeth LLC*, No. 09-152 (Feb. 22, 2011), that the Vaccine Act of 1986 bars state-law design-defect claims against vaccine manufacturers, this Court reiterated that "we have previously expressed doubt that Congress would quietly preempt product-liability claims without providing a federal substitute." No. 09-152, slip op. at 16 (citing *Lohr*). In *Bruesewitz*, this Court observed that, in enacting the 1986 Vaccine Act, Congress deliberately departed from the regime applicable to pharmaceuticals and established a "no-fault compensation program 'designed to work faster and with greater ease than the civil tort system.'" *Id.* at 3 (citation omitted). In contrast, there is no similar no-fault compensation scheme available with respect to generic drugs, and no indication that Congress sought to displace traditional state-law tort remedies.

Establishing a categorical preemption of all state law claims against generic drug manufacturers would

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[11] *Riegel v. Medtronic, Inc.*, 552 U.S. 312 (2008) (considering the effect of the express preemption provision of the Medical Device Amendments of 1976, 21 U.S.C. § 360(k)(a)).

[12] *Bruesewitz v. Wyeth LLC*, No. 09-152 (Feb. 22, 2011) (construing 42 U.S.C. §300aa-22(b)(1), enacted as part of the National Childhood Vaccine Injury Act of 1986).

[13] In 1997, Congress preempted certain state requirements concerning over-the-counter medications but expressly preserved product liability actions. *See* 21 U.S.C. §§ 379r(e), 379s(d).

create a dangerous asymmetry because it would make the availability of a compensatory tort remedy depend upon the fortuity of whether a patient receives a prescription for a name brand or generic drug. In enacting the Hatch-Waxman Amendments, Congress did not intend to create a categorical exemption from failure-to-warn liability for generic manufacturers.

CONCLUSION

The judgments below should be affirmed

Respectfully submitted,

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PETITION FOR RE-HEARING

Supreme Court, U.S.
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JUL 18 2011
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NOS. 09 - 993, 09 - 1039, & 09 - 1501

IN THE

Supreme Court of the United States

PLIVA, INC., ET AL., *Petitioners*,

v.

GLADYS MENSING, *Respondent*.

ACTAVIS ELIZABETH LLC, *Petitioner*,

v.

GLADYS MENSING, *Respondent*.

ACTAVIS, INC., *Petitioner*,

v.

JULIE DEMAHY, *Respondent*.

On Writs of Certiorari to the United States Courts of Appeals for the Eighth Circuit and for the Fifth Circuit

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RESPONDENTS' PETITION FOR REHEARING

Respondents Gladys Mensing and Julie Demahy hereby respectfully petition the Court to rehear *Pliva, Inc., v. Mensing*, No. 09-993; *Actavis Elizabeth, LLC v. Mensing*, No. 09-1039; and *Actavis, Inc. v. Demahy*, No. 09-1501. Respondents seek rehearing because the judgment of the Court rendered on June 23, 2011 does not follow from the rule announced by the Court in this case. The Court overlooks the fact that the Petitioner generic drug companies could have "independently" complied with both state and federal law simply by suspending sales of generic metoclopramide with warnings that they knew or should have known were inadequate.

DISCUSSION

In the Opinion of the Court, this Court announced a new test for implied conflict preemption based on impossibility: "The question for 'impossibility' is whether the private party could independently do under federal law what state law requires of it." *Pliva, Inc. v. Mensing*, No. 09-993; *Actavis Elizabeth, LLC v. Mensing*, No. 09-1039; *Actavis, Inc. v. Demahy*, No. 09-1501, 2011 WL 2472790 (U.S. June 23, 2011), at *10 (citation omitted). The Court reasoned that "State tort law . . . required the Manufacturers to use a different, stronger label than the label they actually used," but that "Federal drug regulations, as interpreted by the FDA, prevented the Manufacturers from independently changing their generic drugs' safety labels." *Id.* at *8. Therefore, because the Manufacturers could not independently change their labels, the Court found Respondents' failure-to-warn claims preempted.

But the Court's logic is erroneous, because it begins with a false premise. Contrary to the Court's reasoning, neither Minnesota nor Louisiana law required the Manufacturers to change their labels. Instead, what state tort law required was that the manufacturers not sell a drug that lacked adequate warnings. Resp'ts' Br. 29. The Petitioners could have satisfied this state law duty in either of two ways. As the Court recognized, Petitioners could have satisfied that duty by strengthening their warning labels; but that course of action required FDA approval and therefore could not have been accomplished independently. Alternatively, however, Petitioners could have satisfied their duty under state tort law by suspending sales of the product with a label that they knew or should have known was inadequate. *See Mensing v. Wyeth, Inc.*, 588 F.3d 603, 611 (8th Cir. 2009) ("The generic defendants were not compelled to market metoclopramide. If they realized their label was insufficient but did not believe they could even propose a label change, they could have simply stopped selling the product"). That course of action was always available to them and could have been accomplished independently, without any action by the FDA.[1] Thus, it was not impossible for the Petitioners to comply with both federal and state law: they "could independently do under federal law what state law requires of" them.

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[1] Suspension of sales by the manufacturers of generic metoclopramide would not have risked injury to users of their products who needed access to the drug, because the name-brand product, Reglan, remains on the market. And the manufacturer of Reglan could have added an adequate warning to its label through the CBE process. *See Wyeth v. Levine*, 555 U.S. 555, 129 S. Ct. 1187 (2009); 21 C.F.R. § 314.70(c)

A decision by Petitioners to stop selling generic metoclopramide with inadequate safety warnings would not only have satisfied their duties under Minnesota and Louisiana tort law; it would also have complied with their duties under the Federal Food, Drug, and Cosmetic Act (FDCA). As Justice Thomas noted in his concurrence in *Wyeth v. Levine*, "the statutory provisions governing FDA drug labeling, and the regulations promulgated thereunder, do not give drug manufacturers an unconditional right to market their federally approved drug at all times with the precise label initially approved by the FDA." 129 S. Ct. at 1210 (Thomas, J., concurring). Federal law prohibits the sale of misbranded drugs, 21 U.S.C. § 331, and deems a drug to be misbranded if it lacks "adequate warnings." 21 U.S.C. § 352(f)(2). Thus, Respondents' state law failure-to-warn claims "parallel" the duties imposed on drug manufacturers under federal law. This Court has repeatedly held that such parallel claims escape preemption, even under statutory schemes with express preemption provisions. *Riegel v. Medtronic, Inc.*, 552 U.S. 312, 330 (2008); *Bates v. Dow Agrosciences LLC*, 544 U.S. 431, 447-48 (2005); *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 495 (1996). Indeed, so far as Respondents are aware, the decision in this case represents the first and only time this Court has ever held a traditional state-law cause of action preempted where the duties imposed by that cause of action were parallel to requirements imposed by federal law.

The ruling of this Court rested on a false premise regarding the duties imposed by state law; the actual state law duties paralleled federal law and could have been satisfied by Petitioners independently, without any action by the FDA or any

other party. This Court should therefore rehear these cases in order to address this error in its reasoning.

CONCLUSION

For the foregoing reasons, Respondents Gladys Mensing and Julie Demahy urge this Court to grant this petition for rehearing.

July 18, 2011 Respectfully submitted,

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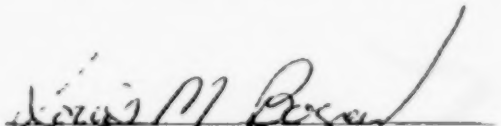
RESPONDENTS' RULE 44.1 CERTIFICATION OF COUNSEL

As counsel of record for Respondents Gladys Mensing and Julie Demahy, I hereby certify that this petition for rehearing is presented to the Court in good faith and not for purposes of delay.

July 18, 2011 Respectfully submitted,



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